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Reed Smith's Nanotechnology Teleseminar Transcription

Jennifer (Operator): Hello and welcome to Reed Smith's Nanotechnology Teleseminar. All participants will be in listen-only mode. There will be an opportunity for you to ask questions at the end of today's presentation. If you should need assistance during the conference, please signal an operator by pressing star and zero on your touch tone phone. For your information, this conference is being recorded. At this time, I would now like to turn the conference over to Tony Klapper. Mr. Klapper, you may begin.

Tony Klapper: Thank you very much, Jennifer. Good morning, everyone. As Jennifer indicated, my name is Tony Klapper. I wanted to invite and welcome you all to Reed Smith's first Nanotechnology Teleseminar, New Environmental Health and Safety Developments: The Silver Nanoparticles Case Study. We intend this to be the first in a series of Teleseminars on issues relating to Nanomaterials, including one teleseminar where we hope and anticipate having a member of Congress discuss legislative initiatives in the area of nanomaterials.

Today we have four speakers. None of whom, I believe, have yet been elected to public office, and I would like each of them to briefly introduce themselves. Jim?

Jim Kosch: Good morning, everybody. My name is Jim Kosch, I am partner in the environmental section at Reed Smith. I am resident in the Princeton and New York offices. My practice focuses on environmental litigation, toxic tort litigation, and environmental regulation. I am also the chair of the ABA Toxic Tort and Environmental Law Committee. Peggy?

Peggy Sanner: Thank you, Jim, and good morning. I am Peggy Sanner, counsel in the product liability section at Reed Smith, and in its Richmond office. My practice over the last twenty years has focused on product liability, toxic tort, and environmental matters, and I have litigated cases concerning pharmaceutical and medical devices, asbestos, particulates, water contamination, and related matters in jurisdictions throughout the country.

Paul Llewellyn: Good afternoon from the United Kingdom. I'm in the Birmingham office of Reed Smith, and I am the UK head of product liability, and

my practice is exclusively in the defense of product liability claims, and in advising companies on regulatory matters.

Tony Klapper: Thanks. Again, my name is Tony Klapper. I am a partner in the Washington, DC office of Reed Smith. My practice as well focuses on products liability, toxic tort issues, and consumer fraud claims. I have previously written and spoken on issues relating to nanomaterials, and at this point we are going to turn the discussion over to Jim, followed by Peggy, then myself, and Paul, and we welcome questions at the end. Jim?

Jim Kosch: Thank you, Tony. For those of you who are following along with the printed or emailed slides, or if you printed them, we will start with the first slide – brief overview.

This subject is one of those in which there is a lot to say, and a little to say at the same time. A lot to say because there are so many complex and interesting technical, scientific, legal, and policy issues, and so little to say because so little is known about the environmental effect and toxic effect of these materials, and where regulation – fair regulation may go. But, let's put it in context. As of today there are some 40 to 50 consumer products using nanoscale silver. One of them is the Samsung Silver Wash washing machine. As suggested by the name, it is a washing machine that is for cleaning of clothes, and it operates by using cold water only and cleans clothes though the use of silver ion particles which are injected in both in the wash and the rinse cycles to kill microbes and bacteria. The goal here is to clean your clothes as well as we do with hot water and detergent, but saving the cost of the hot water, which is a major energy savings. The product is marketed around the world, and has been fairly well received here in the United States.

When there were some first challenges to the product, because it is well established that silver does have some toxic effects, hence its use in killing bacteria and microbes in this circumstance. The EPA through FIFRA determined while the washing machine is not a pesticide, it is a device, meaning a self contained unit that uses physical or mechanical properties to contain pests. Environmental groups and organizations affiliated with clean water authorities weren't happy with this, because they saw that the machine did release silver ions, and there was a potential for those ions to get into the environment either through the discharge of the rinse water, or

from release from the clothes later on. And that those silver particles could get into the water, and then effect plankton, and the food chain - - up, up scale - - or, it could effect the treatment authorities' silver guidelines for clean-up. The issue was brought back to the EPA by way of petition, the EPA on reconsideration determined that, yes, this product should be regulated as pesticide, and is the process of preparing a regulation to that effect. What this will do is subject the manufacturer, Samsung, to the registration and information gathering requirements of FIFRA, which we will discuss a little later in this talk.

What the Samsung issue does is crystallize the need for understanding of where nanotechnology fits within the broad scheme of environmental regulation. As of today, there is no federal statute that regulates nanotechnology from an environmental perspective, as such. Some states talk about it, but they are not doing much either. I have had conversations recently with regulators in the Mid-Atlantic and New England states who basically say "we are not even thinking about this, we are waiting for the Feds. Now to the credit of the government, the EPA in particular, industry, and to some of the NGOs, folks have been giving a lot of thought to the environmental impact of nanotechnology for the about the last four or five years. Most agree we want the benefits of nanotechnology, less waste, better use of energy, and even the use of nanotechnology to remediate industrial pollution from the past. But we don't want to, and they don't want to repeat the mistakes of the industrial revolution.

In the analysis that has been done over the last several years, a consensus has emerged from the government, again industry, and the environmental groups, that the existing federal regulatory structure will work. The definitions of waste are broad enough to include nanotechnology, the identification of responsible parties are adequate, and the means to address at the end are also strong. The problem is, we don't know enough, they don't know enough about the impact of these materials in the environment to address regulation now. The thought had been, because of the economic scale of nanotechnology, and the physical scale of nanotechnology, the real regulatory burdens would come about in about four or five years, that the agencies that would deal with this problem are FDA, and OSHA, and more presently we would learn from them. Well, as this case makes clear, the future is now. And the question is how do we deal with it? I think the short answer, as I go through statutes you'll see, is we are going to as those advising people in industry, people in industry

making decisions, and regulators are going to have to gather information and make informed decisions as we go along.

One of the things I would like to point out, if you are interested, there is an excellent white paper prepared by the EPA on the future of nanotechnology and environmental regulation. It is available on its website, or if you want you can just email me, and I will either send you the link or send you a copy of the white paper.

If we could skip over the next slide, which was environmental regulation in general, let's review some of the particular statutes that are of interest here. Most folks thought that the issue would to fore first with TSCA, the Toxic Substance Control Act. And there is a good reason for that. TSCA is supposed to inventory all existing chemicals, it is supposed to register new chemicals, or deal with changes in new uses of existing chemicals. The issue is, of course, are nanochemicals, nanoproducts, new chemical substance under section five? The answer is no one is quite sure. And that is going to have to be evaluated over time. In general, the industry tends to view this as if the bulk material from which the nanomaterial is made is registered, that is adequate. To the extent a company is going to take that route, I had advised and will continue to advise the company that they should keep specific records on nanotechnology just so that there is a separate stream of information, and they are prepared to deal with issues as they come up, and rather than be surprised. The other, they should look carefully at how their nanoproducts are being used, and if there are changes over time, be prepared to apply for significant new use.

Another interesting reference I would like to send you to, is a white paper done through the Woodrow Wilson Center for Scholars. Their nanotechnology project, it is called Nanotechnology and Regulation: A Case Study Using the Toxic Substance Control Act, which goes in greater detail into the issues I just discussed. It makes for very interesting reading, but as you'll see, there are no real conclusions that can be drawn at this time.

Other statues of interest, are, of course, are the Clean Air Act. It is well settled that the Clean Air Act that the government the ability to regulate the release of emissions, particularly particles. The general view today is that Clean Air Act fine particles regulations would include nanotechnology. The general thought, though, is that the

industry is "too small", pun intended, to have significant air emission impacts, however the information gathering provisions of the Clean Air Act under permits and elsewhere, I think we will see significant use as the government tries to learn more about the release of nano -- particularly as we learn more about respiration problems, and possible toxic effects in the lungs.

RCRA. Again, this is a statute in which nanotechnology is not specifically addressed, but the definition of a listed hazardous waste, or a hazardous characteristic is sufficiently broad that if a nano product or a waste were determined to meet either the listing requirements or the characteristics, the statue would apply and you would be subject to regulation the same as if you were a generator in all other respects.

One point, there has been a recent survey, I think it was done by Icon, folks in the in the nanotechnology business, and running about two to one, and those who are making nanoproducts and generating nanowaste are listing the material as hazardous waste if the bulk source is also a listed waste, but are not identifying the waste as having nano properties. In part, because no one quite knows if there is any difference in the environment, and it hasn't led to any problems to date. But that is something I think industries got to think about in the future, is listing whether or not the content of some hazardous waste may also have a nano aspect.

Moving on to the slide, the Clean Water Act. Much like the Clean Air Act, there is general agreement that the statute will cover nanowastes if they are deemed to be pollutants. The interesting question here is, "How will guidelines be established, and limitations established?"; because we don't know that much about the performance of these materials in the environment. The key issue, I think folks need to look at it, is really from a non-point discharge perspective, because the way the product is being introduced into the economy, and then into the waste stream is more . . . as Samsung makes clear, is more likely than not, it will be from non-point sources. I don't think the government is ever going to contend that your washing machine is a point source requiring a NPDES permit.

CERCLA, next slide. CERCLA, like RCRA does not specifically define, or have a category of hazardous waste that would include nanowaste, but if at some point it is determined that a particular nano

product is a hazardous waste, CERCLA would apply the same as if any other hazardous waste was involved. The interesting question here, is, what would be a reportable release, and what would be an appropriate remediation?

The next slide, NEPA, National Environmental Policy Act. People kind of view this as a "catch-all" if there is significant federal involvement in nano project, and with the National Nanotechnology Initiative, and the funding that goes with it, I guess that day is coming. The point with NEPA is, if there is a federal involvement, there may be a need for EIS. If there is an EIS, is may be basis for groups opposed to this technology to tie up at least those projects, and raise other questions.

Finally, FIFRA. FIFRA is where this case comes to full bore. Under FIFRA the EPA has authority to regulate pesticides even before any registration is required. We are beyond that, at least in this particular case, and we look to section three, on pesticide registration, and here the law is very clear and very precise. No one may distribute or sell a pesticide unless registered under this section, and it is the function, not the format of the material that controls. Now, if once this regulation for Samsung kicks in, the government has several options here. As part of the registration it can require Samsung to generate data for a risk assessment, it can require Samsung to do the risk assessment, it can do it itself. It can prohibit the product, or it could condition its use on various things, including gathering information. My view here is that this registration will require a conditional use, and will require gathering of data, and I understand Samsung has done a fair amount of data to determine this risk assessment, but more needs to be done. There is a foundation for this, in that the EPA through FIFRA already strictly regulates genetically modified pesticides, so I think that is the route we are going to go here.

And to the next slide, FIFRA raised by the EPA notice. What might this mean to Samsung? I think I just answered that question. It is going to be more study, more information gathering, but I think the product is going to stay out on the market. The next question, is the interesting on that is going to be studied, and that is, is nanosilver different than its larger-sized cousins? That is an open question, and what its effects are have yet to be determined, and Peggy will touch on that in a minute. If you are a company that makes a nanosilver product making pesticidal claims, this makes absolutely clear that I

think you should register and take a proactive role in getting in there to register and doing your research. If, as is the case with one company, you made a pesticidal claim, and then when this brouhaha hit, you withdrew it, I think you should do, my view, the wise thing, is go back to the fact that you made a pesticidal claim, register one, you get to market it with that claim, why else would be putting the silver in? Two, you get the benefit in the marketplace of that. Because otherwise, it is acting as a pesticide, the government has the authority to come after you, and you don't want to be the company that gets a knock on the door "I'm from the government, we're here to help." So, if it acts like a pesticide, follow the law in that regard.

With that said, having given a very quick overview of the statutes that might apply, I would like to turn it over to Peggy to discuss some of the environmental issues related to exposure, environmental fate, and toxicity. Peggy?

Peggy Sanner: Thank you, Jim. As Jim indicated there is now a burgeoning number of potential and actual nanomaterial applications, prominently exemplified by Samsung's use of nanosilver in washers. These uses have captured the imagination of engineers, doctors, physicists, and others across a broad spectrum. Yet, researchers in the field continue to remark on what they characterize as a serious lack of information concerning the human health and environmental implications of these manufactured nanoparticles. The reported studies including some on nanosilver in particular suggest significant human benefits. But they also indicate the potential for environmental and health risks.

And moving on, past the fish, the picture of the fish, to questions about whether or not nanoparticles in the silver format will kill the fish? I note that the question is raised because of the known toxicity of non-nanosilver in the aquatic environment as a first threshold. In a recent fish and amphibian toxicity study involving 22 metals, for example, silver, especially in its ionic form, was the most toxic tested element. A notable instance of silver's toxicity can be seen in the instance of silver forming part of mining runoff, which is considered to be the culprit in an earlier decimation of the clam population in San Francisco Bay. But, there is some basis now in the literature for postulating that nanoscale silver is more toxic than non-nanosilver. The chemistry is the first place where this possibility is suggested. Nanoparticles toxicity, is potentially influenced by a number of properties which are particular to the nanoscale formed. Their size,

there shape, their surface characteristics like charge, area, and reactivity, just for few examples. Some nanoparticles are small enough to allow passive diffusion of these particles into fish gills. With respect to charge, nanoparticles may be neutral, negative, positive, or have characteristics of both, and the charge effects the ability and propensity of these particles to bind to other materials. Neutral charged nano may bind preferentially to organic materials. Positively charged particles including some nanosilver forms, may more easily bind to and thereby potentially damage cell membranes. The larger surface area to mass, which is characteristic of nanoparticles indicates a high potential of these particles to absorb to or attach to a suspended soil and sediment particles, and it may well indicate a probably ability of these particles to penetrate cells more easily, and in a different manner than larger particles of the same chemicals.

Moving to the next slide, I would like to bring your attention to some in vitro studies which have been done with nanosilver exposure. The first study involves the exposure of a mouse sperm stem cell line to three different kinds of nanoparticles; silver, molybdenum, and aluminum. The researchers reported, from this study, a concentration dependent toxicity for all nanoparticles tested, in contrast to the corresponding larger particles which had no significant side effect. Silver nano was characterized as drastically reducing cell viability and interfering with cell metabolism. The same et. al also studied potential toxicity of nanosilver in vitro to a line of rat liver cells. They found that silver was the most toxic of the seven nanoparticles tested, and that larger silver nano particles at a hundred nanometers were more toxic than smaller ones at fifteen. Cells exposed at higher doses became abnormal, displaying both cellular shrinkage and irregular boundaries. The same et. al also exposed a rat neuroendocrine cell line in vitro to nanosilver and nanomanganese oxide, and they reported in this study as well findings of cell shrinkage and irregular membrane boarders together with a decreased mitochondrial function for those who were exposed to nanosilver. It is well known that chemicals react somewhat differently when applied in vitro, as opposed to being introduced to cells in an in vitro environment. Problems that appear in the former do not necessarily show what would arise in the latter environment. But these studies indicate areas of uncertainly concerning nanosilver's potential toxicity to organisms and the need for further research.

I also would like to point out that research has been conducted, at least in preliminary stages with respect to nanoparticles' effect on larger organisms. These studies are typically involving nanocarbon, not nanosilver, and other nanoparticles, but again, they are suggestive of avenues of research and potential questions that need to have answers. Eva Oberdorster studied the effect on plankton, of course the principle food source for larva and fish, by exposure to carbon fullerenes. She concluded that there was toxicity when exposed at relatively low part per billion concentrations. She also, in later studies, reported that juvenile large-mouth bass when exposed to carbon nanoparticles showed significant oxidative stress in brains, liver, and gills. There was also evidence of depletion in these bass of an important gill enzyme. Zebra fish, as reported by Chang and Chang gave evidence of reduced hatching rates when they had been exposed for some period to carbon nanotube aggregates. All of these studies, again, indicate the need for comprehensive research involving nanoparticles in general, and nanosilver in particular.

If it is determined that nanosilver, and I am moving on to the next slide, is toxic to plankton and fish, it is critical to know whether, and the extent to which nanosilver can be removed from water before exposure occurs. The activity of nanosilver in water treatment systems is not fully known at this time, but the of the usual treatment processes, several appear likely to effect nanoparticles, and in a variety of ways. Smaller nanoparticles are expected to settle more slowly, giving them a longer time in which to interact however they will in the aquatic environment. Absorption rates may be higher for nanoparticles then for non-nano, given their higher surface area to mass ratios. Complexation by natural organic chemicals may facilitate reactions that will have the effect of immobilizing nanoparticles. So, some characteristics of nano-sized particles suggest that there will be enhanced possibility for environmental remediation. But their efficacy with respect with to the removal of nanosilver is not known.

Exposure to the biomass is an important treatment pathway for contaminated water. Will the biomass processes help to break down or mobilize nanosilver given its biocidal and antimicrobial propensities? On the macro level it is known that alpha biomass has the ability to take up non-nanosilver ions from contaminated water. The microbial biomass, which is a key aspect of the aerobic treatment of wastewater, has promising possibilities for treating water

contaminated with nanoparticles. It has been reported, for example, that microbial aggregates are able to remove some nanoparticles, fluorescent microspheres from the wastewater. Will this work for nanosilver? In this connection I simply refer to a recently filed patent application which relies on nanosilver specifically for its biocidal qualities. This application would use nanosilver in construction products to protect those products from the adverse effects of bacteria, fungi, molds, algae, and other bioorganisms. These, and similar applications, again, require investigation of the extent to which the microbial biomass in natural systems and in treatment systems will be able to immobilize nanosilver in the waste water, or instead be destroyed by it.

Now, it is important to emphasize just how exciting are the possibilities which are now being reported in the use of nanosilver to justify why one should undertake the research that I believe is required. Non-nanosilver has, as we have indicated, important antimicrobial qualities harnessed for years in medical applications, such as silver salts, which are nitrate and silver sulfide dioxide used in _____ burn and chronic wound treatments, and in coatings to be attached to medical devices such as catheters and stints. But nanosilver may dramatically improve these applications. In the treatment of burns the antimicrobial action of silver depends on the emission of free silver ions into the wound fluid. Silver salts, traditionally used, quickly interact with, and their ions are rendered ineffective by the organic matter and other chemicals in the wound fluid. That required, therefore, a continuous replenishment by frequent changing of the dressings, which has some obvious pain-related side effects in burn victims, and may also hinder treatment. However, the reported new uses of silver in its nano form include bandages which are impregnated with neutrally-charged silver in a nanocrystalline form, which is said to yield a steady slow replenishment of silver nanoparticles, which are far less actively activated by the wound fluids, chloride, and organic matter. Reportedly, this form of nanosilver may continue its antimicrobial work for up to seven days, during which the bandage need not be changed, and during which many other significant benefits vis-a-vie earlier silver salt treatment are obtained. In addition to this use for the treatment of wounds, numerous other potential antimicrobial uses of nanosilver are being proposed, such as in bone cement, and

implantable devices. No human toxicity has yet been demonstrated for these nanoscale uses of silver.

In conclusion, I would just like to summarize that these reported studies involving nanoparticles, in many cases nanosilver, demonstrate both tremendous promise, but also potential toxicities which are as of yet not fully understood. Comprehensive research is needed critically to facilitate understanding of how nanosilver in all of its different sizes, charges, and forms will interact in the natural and human environments.

With that, I would like to turn the program over to Tony Klapper, who will address some of the risk mitigation concepts appropriate in this era of scientific uncertainty. Thank you.

Tony Klapper: Thank you, Peggy. As Peggy pointed out, and frankly as also Jim pointed out, the key with all nanomaterials, not just nanosilver, is that the science is either not yet developed, or frankly, is inconclusive. Notwithstanding that, in the face of this uncertainty, we feel there are steps that companies can still take to mitigate their risk. I've divided this into three recommendations regarding ways to mitigate risk -- monitor, avoid, and respond.

Moving to the next slide. With respect to monitoring – monitoring refers to evaluating the risk and monitoring what people are doing about it. First, companies should monitor and track the ever expanding science. We're not suggesting that companies need to subscribe to every scholarly, medical, or scientific journal, study those journals and identified the takeaways that effect nanomaterials that are at large. But it does mean that you as a company will be held accountable for knowing what's been said about the specific nanomaterials used in your product, particularly if that information is available within the public domain. Thankfully there are resources that have collected, or have attempted to collect information from the medical and scientific literature that may help separate the scientific chaft from the scientific wheat. For example, the International Nano Health Information Network, and NIOSH's Nanoparticle Information Library, are two databases of information that companies should be aware of.

Second, companies should monitor and track what the regulatory community is saying and doing. Most companies, and we know this

from our attendance at multiple conferences, are begging for some regulatory guidance, some predictability. While there are no regulations yet, and as Jim pointed out, they are imminent, you don't want to be caught flat-footed. In fact, you may even want to participate in the deliberative and the investigative process of these regulatory agencies. EPA, NIOSH, and FDA have all recently sponsored conferences to discuss environmental health and safety issues relating to nanomaterials. There are, of course, agency websites that contain lots of information, and you can sign up for email alerts from many of those same agencies. The bottom line is, it is important to understand where the regulatory agencies are going on these issues, and track it some way and in some form.

In addition to what the regulators are doing, you should also know what industry is doing. You want to be careful about falling behind what other companies are doing in this arena. Particularly in the environmental health and safety arena. If your practices are not up to industry par, you are exposing yourself to some additional liability exposure. Not all companies, as we know, will share their practices with their competitors. But groups like, as Jim pointed out earlier, Icon have surveyed current practices and reported those findings which are available to the public. EPA is similarly trying to secure similar type of information. In addition to regulatory agencies and other companies, there are of course the non-governmental and quasi-governmental groups who should also not be ignored. For example, there is the International Council for Technology Assessment (CTA). CTA was the lead drafter of a petition filed last spring with the FDA seeking to put a moratorium on the sale of sunscreens and cosmetics. CTA's website contains a series of so-called "red flags" identifying substances they claim present an excess risk of harm to humans and to the environment. The Woodrow Wilson International Center for Scholars, a combined quasi-public organization is another source. The Center frequently writes and speak about nanotech issues and recently the head of its nanotech program, Dr. Andrew Maynard, and other scientists wrote a commentary in Nature magazine highlighting, amongst other things, the asbestos-like qualities of some nanomaterials. Those with high aspect ratios such as carbon nanotubes, nanowires, and nanofibers. Knowing the pressure points of these organizations, organizations that work closely with or in some instances are antagonistic to federal agencies, will help

companies know where to focus their energies and where to implement prophylactic measures.

In addition to looking outside, companies should also look internally, which brings me to the next bullet. Companies should consider monitoring and tracking their workforce, their consumers, and the environment by having effective reporting systems in place. We are not advocating medical monitoring. Not only may it not be practical, because you don't know what you are looking for, but it also may very well be unethical. But careful consideration should be given to ways to at least be sensitive and responsive to environmental health and safety concerns amongst workers, customers, users, and the environment itself. Monitoring refers to what you should review.

The next risk mitigation precept we abide to, and propose, is what you should say, and what you should not say. This is drawn from lessons learned from companies who, frankly, have paid dearly in the form of poor reputations, and indeed punitive damages. That advice is avoid communication disconnects. Make sure there is consistency between what your company's internal documents say, and what you say publicly. Reporting on your website that a type of nanomaterial used in your product is "perfectly safe," had better be consistent with your internal correspondence, your internal memos on these same issues. Similarly, make sure that what the science says is consistent with what is stated publicly. This is what I call the lesson on absolutes. Avoid saying that there is "no risk." Particularly when the science is equivocal or incomplete. If indeed its been establish that the risk is de minimus or there is no risk, then say so. But when the science, as if the case predominately in the area of nanomaterials, is still a subject of discussion and analysis making absolutes is problematic.

Additionally, although many times justified because of different regulatory requirements, a global company that employees different environmental health and safety practices, and product stewardship practices in one country may implement different ones in another country, and subject and open itself to criticism and additional scrutiny. This may be an extreme example, but if you take steps, for instance, to reduce the toxicity of nanomaterial affluence coming out of a manufacturing facility in Sweden, but do not do the same in the United States, you are exposing yourself to potential greater liability in the United States. Again, differences in how you handle these

issues, differences in environmental health and safety practices, and in product stewardship practices may be justified due to different regulatory requirements. But you need to think long and hard about your rationale and your exposure risk before adopting different practices. One thing to remember, in the world of products liability and toxic torts, regulatory requirements are more often then not floors, not ceilings.

Finally, avoid complacency. Respond to known or potential risk. Which brings me to my final slide. In responding, first ensure compliance with any existing analogous or reasonably anticipated regulations. Although, as both Peggy and Jim have indicated, there are no regulations directed specifically toward nanomaterials, the Samsung example demonstrates that these regulations are not very far off. In the absence of rule making, look at what the regulators are saying. But also consider turning for guidance to the environmental health and safety practices employed by companies that handle arguably comparable substances. Be it asbestos, ultra-fine chemicals, aerosols, etc.

Second, based on the advice from regulators, scholars, and frankly from your own experiences, take proactive steps to minimize exposures, minimize toxicity by evaluating your products through their entire life cycle. This could begin at the very early stages of design. Determine whether the nanomaterials used in your products are truly encapsulated or bound within some matrix, and think about ways in which the nanomaterials might be released from the matrix. Be aware of scientific studies that talk about coatings and other substances that are purposefully designed into nanomaterials to reduce their toxicity. Within the workplace, considering engineering controls and personal protective equipment that have been used, again, with analogous substances. There is a full spectrum there, some are very costly and intensive, such as clean rooms and closed systems, others are less intensive, and may be frankly, and likely, are less protective, but nonetheless may be appropriate in a given circumstance. For example the disposable types of personal protective equipment, like dust masks, and gloves. Consider the environmental issues, disposal practices, take-home exposures, and the like.

Third, implement risk communication strategies. We are not talking about product warnings per say, but reevaluate your MSDS sheets,

educate your workers, and think carefully about whether to disclose to the outside world that your products contain engineered nanomaterials. On warnings, it is premature to issue warnings at least in the United States if there is no demonstrated risk unique to the materials because of their nano-sized shape, and size.

Fourth, take all complaints and inquiries seriously. Be prepared to adapt to changes required, again, by common sense.

Finally, know your reporting obligations. Both domestic and international. If there is a problem, you should have in place a system that you can quickly refer to, that directs you to whether you need to advise EPA, OSHA, FDA, or some agency, or indeed some international group about that problem. Which brings us, speaking of international, to our fourth speaker, Paul Llewellyn. Paul?

Paul Llewellyn: Thank you, Tony. If you look at my first slide, you will see that the subject is nanotechnology and the EU. Because of the scientific and legal uncertainties and the limited time available, I am not going to deal with the substantive law. I will look at the economic and regulatory context in which nanotechnology is developing in the EU.

The EU is regarded by many US manufacturers and their lawyers as a rapidly expanding collective organization of disparate states whose language, culture, institutions, and economic performance vary enormously. As of January 2007 there are now 27 member states of the EU. There is also a widespread different view of the EU, a perception that it is overregulated, and is becoming more so. The REACH regulation, the registration, evaluation, and authorization of chemicals will take effect in July 2007, although the transitional arrangements will take many years to complete. It is thought to be the apotheosis on nadir, depending on your viewpoint, of a regulatory impulse that is vigorous or out of control, again depending on your viewpoint. The regulation runs 846 pages. It has been hailed or condemned, according to preference, as the largest and most complex legislation to be introduced in Europe.

Another _____ of those who see the EU regulatory regime as overblown, and antithetical to business is the precautionary principle, the principle that determines when regulatory action is instituted by the EU, or by member states. A Washington legal foundation report of November 2006, by Lawrence Kogan of the Institute for Trade

Standards and Sustainable Developments, was entitled Exporting Precaution: How Europe's Risk Free Regulatory Agenda Threatens American Free Enterprise. The report describes how, and I quote "international bureaucrats and influential activist groups used the precautionary principle as a vehicle to diminish America's competitive position in the global economy, and advance special interest agendas hostile to free enterprise and technology." It all looks rather grim for nanomaterials in the EU, you might think in the circumstances.

Let's see what the EU policy actually is on nanomaterials. The European commission published a report in 2004, entitled Towards a European Strategy for Nanotechnology. It estimated the total public expenditure in the EU, which then stood at 15 member states as opposed to the current 27, was 1.5 billion U.S. dollars. The U.S. public expenditure on nanotechnology was estimated to be 1.1 billion dollars. The report noted that Europe had invested early in nano sciences and technology, and had established a strong knowledge base. The report went on to state that the goal of Europe was to become the world's leading knowledge-based economy within the current decade, and it was therefor essential that industry should bring nanotechnology based products and services to the market, so as to generate wealth, employment, and sustainable growth. The report recognized that it was crucial that a favorable environment be created for nanotechnological innovation, whilst dealing with any negative impact on public health, public safety, or the environment. The report identified five dynamics to stimulate progress of nanotechnology; research and development, European polls of excellence, investing in human resources, industrial innovation, and "integrating the societal dimension" a rather pretentious and pompous way of saying that development of nanotechnology must be responsible and have regard for public safety, and health, and the environment.

The next slide refers to the June 2005 European Commission publication, Nano Sciences and Nanotechnology: An Action Plan for Europe, 2005-2009. This described EU level initiatives to reinforce R & D in nanotechnology and propose a doubling of the EU budget for that purpose. It called upon member states to increase public investment in R & D, and to coordinate their R & D at national and regional levels. The document sets out very specific policy initiatives and proposals for each of the five dynamics of the 2004 report.

The founding treaty of the EU, the Treaty of Rome, has a fundamental principle - A high level of protection for the public and the environment. Consistent with this principle, the action plan for nano sciences and technologies envisages risk assessments integrated at all stages of the life cycle of the technology; starting at the point of conception, and including R & D, manufacturing, distribution, use and disposal, or recycling. Appropriate assessments should carried out, and risk management procedures elaborated before, for example, commencing the mass production of engineered nanomaterials. The policy requires particular attention to those products that are already, or are close to being on the market, such as household products, cosmetics, pesticides, food contact materials, and medical products and devices. The policy envisages that the REACH regulation, when it is finalized, "may cover some aspects on nanoparticles produced in very high quantities, but until REACH is adopted, the notification scheme and the directive 67/548/EEC will apply for new substances and notified substances with new uses." There is plainly therefore a degree of uncertainly at commercial level, as to the precise impact of REACH on nanotechnologies. Over all, the EU policy seems to me, to be appropriately balanced between the desire to exploit nanotechnology and to make it part of a successful and vibrant economy, whilst ensuring that appropriate regard is had for the safety of the public and the environment. The policy, in fact, seems very similar to that emerging in the U.S.

Does the precautionary principle threaten the implementation of the EE policy? This is on the next slide. The precautionary principle has three essential strands. First, any assessment of the risk to environmental and human safety should be based on scientific and technical data. Secondly, recourse to the principle requires identification of the potentially negative effects of any technology, and a scientific evaluation of the risk which, because of the insufficiency of the data, it's inconclusive or imprecise nature makes it impossible to determine with sufficient certainty the true nature and extent of the risk. Thirdly, and finally, in determining whether to invoke one of the wide range of actions available under the precautionary principle, decision makers must act proportionally and consistently after examining the benefits of action or inaction. It is easy to cite instances of the questionable application of the precautionary principle, but the principle itself is unexceptional. It represents a balanced approach, and in rapidly developing

technological world, with a myriad of risks, it is entirely appropriate. The diagnosis of Lawrence Kogan, that the precautionary principle is a threat to American free enterprise seems in the context risible, and hyperbolic. My view is, is that the precautionary principle, particularly as it has evolved in an EU, ever conscious of the need to maintain competitiveness in a global market will not in practice be an inappropriate or hindering criterion for the assessment of nano sciences and nanotechnology.

My last slide, concerns REACH. It is not possible in the limited time available to give any details about the very formidable REACH legislation. The regulation was only finalized in December 2006, and it is now the task of industry, lawyers, and regulators to review and comprehend the regulation. It will, however, certainly have an impact on nanotechnology, since the regulation covers not only chemicals as pure substances, but also preparations, that is a mixture of chemicals. . . . also, manufactured goods designed to emit chemicals during use.

My conclusion, and the essential message that I want to convey to you today, is that the EU is committed to developing leading edge nano sciences and nanotechnology consistent with the legitimate requirement that its development must have proper regard for health and safety, and the environment. And now I'll hand back to Tony.

Tony Klapper: Thank you very much, Paul. To just basically briefly sum-up, and just to direct you to the second to last slide. In the very near future, nanomaterials will be regulated, that is clear. And it is reasonable to assume – emphasize reasonable to assume – that some nanomaterials will be deemed hazardous to humans, or the environment, and that litigation will follow. It is our recommendation to all companies manufacturing nanomaterials to think about ways to mitigate their exposure risk - from a regulatory and a litigation perspective, and to think about those ways to mitigate risk, now, because it makes good business sense.

This concludes our presentation, we invite questions that we will be able to field on this call. If, however, you would like to reach out to us separately, and/or want more details, please contact anyone of us listed on the last slide. We have our email and phone numbers listed. So, questions now - I'll ask the Jennifer, the operator, explain the process to everyone.

Jennifer (Operator): At this time, if you would like to ask a question, please press star and one on a touch tone phone. You will hear a tone to confirm that you have entered the list. If you decide you want to withdraw your question, please press star and two to remove yourself from the list. Again, that is star and then one to ask a question.

Our first question comes from Jespree Grudral? of Exponent. Please go ahead with your question.

Jespree Grudral: Hi everybody! Nice presentation, by the way. It was very informative, and I thank you. Just one quick question. I think it was either Anthony or Jim who mentioned there were two databases on nanosilver that we could tack. Could you mention those names again? I missed them, sorry.

Tony Klapper: Absolutely. One is, and let me pull it up again. One is one that is put out by NIOSH, and what I can do, if you send me an email, I can send you the actual links to these, if you are interested. One was put out by NIOSH, and I am struggling to find the actual site here . . . yeah, one is NIOSH's Nanoparticle Information Library, and the other is the International Nano Health Information Network, which I understand is being developed, and I believe is online at this stage. But I will double check that, and I will forward you the links. Just shoot me an email using, again, the last slide.

Jespree Grudral: Ok. Thank you.

Tony Klapper: You're welcome.

Jennifer (Operator): Our next question comes from Dionysius Dianysou, of the University of Cincinnati. Please go ahead with your question.

Dionysius Dianysou: Thank you. The question I have relates to the monitoring of nanoparticles in the environment. Why we are trying to regulate these nanoparticles . . . may be toxic nanoparticles? Also, one challenge that we may have is monitoring them, especially at very small concentrations. Do you have any ideas about the status about this particular issue? Do we have enough monitoring devices?

Tony Klapper: I am going to ask that Jim try to field that . . . and/or Peggy, and I may weigh in as well.

Jim Kosch: This is Jim. I mean, there are two parts to that question as I hear it. One is, monitoring it from a technical standpoint, which I am not competent at all actually to answer other than to say that from what I have read, I don't think that there is sufficient technology. From the regulatory standpoint monitoring based on what we do have available to us, each of the statutes we went through have one or another information gathering and reporting requirements. I think in the near term, that is how the government is going to proceed. I know from dealing with particular clients, and just following the field, and also hearing what Tony had to say, prudent industry is gathering and monitoring information with the idea of looking down the line to avoid liability. So, to answer the question, again, in summation, technically I think we need to develop more to monitor, and from a legal standpoint, we are going to use whatever we have, or, I think people are going to use whatever is available to gather information and build from there. Peggy, do you have anything?

Peggy Sanner: You, know, I just wanted to add a bit. It is plain that the science for monitoring the effects of nanoparticles in cellular applications, and in vivo is a developing science. Each one of the studies that you read discusses the efficacy of the testing mechanism for reaching the goal that is required. I think that this is an ongoing process.

Tony Klapper: And one final point that I'll add, this is Tony. I do know that there is monitoring that does occur with respect to naturally occurring nanoparticles that is pollution. Andrew Maynard and other articles in Nature, speaks to this very issue, and calls for a collective concerted effort to evaluate ways in which to find proper mechanisms and tools to do this type of monitoring, and if you are not familiar with that article, that commentary that appeared in Nature, I encourage you to take a look. And, again, if you don't have easy access, if you shoot me an email, I can send you a link.

Dionysius Dianysou: Thank you.

Jennifer (Operator): There are no further questions at this time. Would you like me to repeat the instructions once more?

Tony Klapper: Sure.

Jennifer (Operator): Again, if you would like to ask a question you may press star and then one on your touch tone phone. And we have a question from Daryl Boudreaux of NanoHoldings.

Daryl Boudreaux: Yes, it was my understanding that the Food and Drug Administration has permitted some uses of nanosilver in food wrappings and related materials for their antimicrobial properties. Is that true, or not? And if it is true, how does it relate to some of the issues that you were discussing today?

Tony Klapper: I will ask either Peggy or Jim to tackle that one.

Peggy Sanner: As a preliminary matter is it the case that nanosilver is used in certain food wrappings which are now on the market, and certainly the reported results suggest that the antimicrobial properties, as it were, alive and kicking. From my perspective, it indicates, among other things, the recognition that silver in its nano form had antimicrobial properties that will at all points need to be taken into effect, including when the silver goes into the waterways. So, it is an ongoing process, I believe.

Jim Kosch: This is Jim. I'm not fully familiar with that regulation, but I am aware of the use, and there is two things with that. One, under certain statutes there is a tolerance level for human exposure, that hasn't been established for nanosilver, but that is something I think that is going to have to be looked at. Secondly, long term . . . as the volume of these type products increase and their disposal in the waste stream, whether as solid waste or eventually possibly hazardous waste. As that volume increases to the point where there is a threat of more silver, using this example, in the way stream, there is going to have to be some development – ways to deal with that. One of them being repackaging, or changing the mode of packaging. The other thing, I know from other experience from the ink industry, is that there are very well established standards for the types of inks that you can use, that can get in contact, or near contact with foods, and those regulations will probably go parallel to that. He only is, the science is much more developed on the exposure to the components of the inks then it is on this nanosilver. But, by analogy, they will look at macro or bulk silver exposure.

Tony Klapper: And this is Tony. My only final observation here is I don't believe the FDA is doing anything specific to regulate nanosilver _____

nanosilver. In October I was in attendance at the FDA meeting on nanotechnology, and my understanding, both from that as well as subsequent meetings, the NIOSH meeting in Cincinnati, is that it is going to be in July of 2007 that FDA is going to issue any type of report or assessment relating to nanomaterials that are at large, and that report may contain information regarding packaging or repackaging.

Daryl Boudreaux: Thank you.

Jennifer (Operator): And we do have a follow-up from Dionysius Dianysou, of the University of Cincinnati. Please go ahead with your question.

Dionysius Dianysou: The second question I have pertains to the type of solution we have silver. For example, we may have a device that includes nanoparticle silver, or it could be micro particle silver, but the final product that is leeching out of the device is dissolved silver. Does this fall under the nanotechnology type of regulations?

Tony Klapper: Again, I think this is probably best fielded by either Jim or Peggy, or some combination thereto.

Jim Kosch: In that situation it is going to be determined by the amount of silver being detected. Depending on which regulatory scheme you are under, there are various triggers. For example, just this week there were new regulations proposed – at least proposed, it may have been adopted, I'm not quite sure as we speak right now – under the Safe Drinking Water Act for silver in the water supplies. At the point where the silver is measurable, and it kicks into a regulatory regime in place, you have to comply with that. Depending on the scale of the silver, detection becomes an issue. And then, the big question here that everybody is dealing with – lets assume all of the silver being leached is nano. Are there different behaviors and different consequences as a result of those behaviors from that release or discharge? That is the open question, but to answer directly as to the release of silver, it depends on the statute and the quantitative requirement for action.

Dionysius Dianysou: Thank you.

Jennifer (Operator): At this time, there are no further questions. Would you like to make some closing remarks?

Tony Klapper: Sure, once again, thank you everyone for participating in our first nanotechnology teleseminar. As I indicated out the outset, Reed Smith intends to host a series of nanotech teleseminars relating to issues of interest, and we will advise all the folks who decided to participate on today's call of the timing and the substance of any future teleseminars relating to these issues. And again, if folks would like to reach out to us separately and directly relating to specific questions that they may have, questions that may relate to their company or their practices etc., feel free to do so by contacting any one of us through the emails or the phone numbers listed. With that, thanks again for participating.

Reed Smith's Nanotechnology Teleseminar: New Environmental, Health and Safety Developments – The Silver Nanoparticles Case Study

Antony Klapper (Washington, DC)
Jim Kosch (Princeton, New Jersey)
Paul Llewellyn (Birmingham, United Kingdom)
Peggy Sanner (Richmond, Virginia)

January 16, 2007

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Brief Overview of The Issue

- To date, nanoscale silver has been used in over 40 consumer products (e.g. Samsung)
- Environmental groups and wastewater treatment authorities want silver out
- First EPA petition goes nowhere because washing machine deemed a “device”
- Thanksgiving 2006: EPA *surprisingly* switches course on Samsung
- Waiting on FIFRA rule-making

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Environmental Regulation - General

- No existing federal law regulates the environmental aspects of nanotechnology, as such
- Lots of thought given to avoiding the mistakes of the Industrial Revolution
- There is a general consensus that existing laws (i.e., TSCA, CAA, CWA, CERCLA, FIFRA, NEPA) are adequate to address any problems, but *how* those laws should apply to not fully studied nanomaterials is still an open question

PARTICULAR STATUTES

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TSCA

- Section 5 “Premanufacture Notice”
  - Are nanomaterials “new chemical substances”?
    - No one is sure
    - May be other exceptions (early stage applications, low volume manufacturer, low environmental release and test marketing)

TSCA (cont'd)

- Section 5 "Significant New Use"
  - *Same kinds of questions*
- CAS Numbers
- See "Nanotechnology and Regulation: A Case Study Using the Toxic Substance Control Act" (Woodrow Wilson Center for Scholars)

Clean Air Act

- General view is that nanotech industry is presently too small for regulation under CAA
- More needs to be known about respirability and toxicity of nanoparticles
- Statutory Authority to Act
  - Sections 108 and 109 regulate particulates
  - Section 112 classification of nanotechnology industry based on air emissions

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RCRA

- Again, more info needed
- Presently no nanomaterials listed or characterized as hazardous waste
- Assume RCRA would apply if “nanowaste” listed or characterized
  - Generator status
  - TSD
  - Exceptions

CWA

- Could be basis for regulation in Samsung
  - NAWAC contends standards needed to treat nanosilver
- Section 502 defines “pollutant” broadly enough to include nanowaste
- Effluent Guidelines Section 301g(6) and Pretreatment Standards 307(a)
- Effluent Limitations Sections 302, Water Quality Standards Section 303 and 304
- Non-point Discharges Section 319
- NPDES Section 402

CERCLA

- Nanowaste not defined as a hazardous substance
- If it is defined in future, expect CERCLA to apply same as with any other hazardous substance

NEPA

Catchall?

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FIFRA

- EPA has authority to regulate pesticides even before registration is required
  - Test is function not size
- EUP Authority for R&D
  - Section 5 and 40 C.F.R.172 (data submissions)
  - Are refinements needed for nano-based pesticides?
  - Exemptions

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FIFRA (cont'd)

- Pesticide Registration
  - No one may distribute or sell a pesticide unless registered under Section 3
    - Approval for registration controls use
    - Test is "not unreasonably cause adverse effects on environment"
  - Samsung
    - Device v. Pesticide
  - Data submission requirements

FIFRA Issues Raised by EPA Notice

- What might this mean to Samsung in terms of registration requirements?
- Is nanoscale silver different than its larger sized cousins?
- What might this mean to other companies using nanoscale silver and making pesticidal claims?
- What might this mean to companies using nanoscale silver, but removing pesticidal claims? (Sharper Image)

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Nanoscale Silver In The Environment

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Will Silver Nanoparticles Kill All The Plankton and Fish? The Chemistry:

- Silver, especially in ionic form, is a known toxin, and nanosilver *may* be more toxic than non-nanosilver
- Influenced by size, shape and surface (charge, area and reactivity)
  - Charge (neutral, anionic, cationic, amphoteric) may affect binding
  - Surface/mass ratio may increase sorption and cell penetration

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Will Silver Nanoparticles Kill All The Plankton and Fish? *In Vitro* Studies:

- **Spermatogonial stem cells** *Braydich-Stolle 2005*
  - Concentration-dependent toxicity for all nanoparticles
  - Drastic reduction in mitochondrial function and cell viability, increased LDH leakage in nanosilver exposed cells
- **Liver cells** *Hussain, et al. 2005*
  - Nanosilver most toxic of seven, with concentration-dependent increase in LDH leakage and significant cell toxicity. Exposure to all nanoparticles evidenced toxicity.
- **Neuroendocrine cells** *Hussain, et al. 2006*

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Will Silver Nanoparticles Kill All The Plankton and Fish? Tox Studies:

- Nanosilver effects unknown, but studies suggest possible toxicity of nanocarbon to zooplankton and fish
  - Fullerenes toxic to *daphnia magna*. *Obersdorfer 2004 and 2005*
  - Carbon nanoparticles may cause oxidative stress in juvenile bass. *Obersdorfer 2004*
  - Carbon nanotubes may initially reduce zebrafish hatching rates. *Cheng and Cheng 2005*

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Can Nanosilver Be Removed Through Normal Filtration Systems?

- Sorption, chemical reaction and settling will likely affect some nanoparticles
- Microbial granules to remove nanoparticles from wastewater? *Ivanov, et al. 2004.*
- Biocidal effects of nanosilver?
- Fungi, algae and dead biomass take up silver ions and may help break down nanosilver. *See Herrara, et al. 2004.*

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Human Benefits/Toxicity?

- Silver has significant antimicrobial properties and nanosilver offers dramatically promising new therapies
- Burn management with Acticoat bandages. *Edwards-Jones, et al. 2004*.
- Antimicrobial use of silver nanoparticles in bone cement and implantable devices. *Alt, et al. 2004.*
- No demonstrated toxicity of nanosilver to humans

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Key Factors With All Nanomaterials

The science is either:

- Not yet developed or
- It is inconclusive

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In The Face of Uncertainty, however…

There are steps that can still be taken to mitigate your risk:

- Monitor
- Avoid
- Respond

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Risk Mitigation Strategies: Monitor

- Monitor and track the science (databases)
- Monitor and track what the regulatory community is saying/doing (EPA, e.g.)
- Monitor and track what the NGOs are saying (particularly so-called “activist” groups)
- Consider monitoring and tracking your workforce, your consumers, and the environment by having effective reporting systems in place

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Risk Mitigation Strategies: Avoid

- Communication disconnects
  - What the internal documents say versus what is stated publicly
  - What the science says versus what is stated publicly (a lesson on “absolutes”)
  - What is said (or done) domestically versus what is said (or done) in another country
- Being unprepared

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Risk Mitigation Strategies: Respond

- Ensure compliance with any existing, analogous or reasonably anticipated regulations
- Minimize exposures; minimize toxicity
- Implement risk communication strategies
- Take all complaints and inquiries seriously; be prepared to adapt
- Know your reporting obligations (domestic & international)

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Nanotechnology and The EU

- EU Regulation: an attack on US free enterprise?
- A common perception of Europe: overregulated

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The EU Commission: Towards a European strategy for Nanotechnology, 2004

- The goal: a world leader
- The five dynamics:
  - R&D
  - “Poles of Excellence”
  - Invest in Human Resources
  - Industrial innovation
  - “Integrating the societal dimension”

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The EU Commission - Nanosciences and Nanotechnologies: An Action Plan for Europe 2005 - 2209

- EU and MS initiatives
- The safety perspective
  - A high level of public and environmental protection
  - Integrated risk assessments

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The Precautionary Principle, Three Strands:

- Based on science
- When the data is incomplete
- Action must be proportional and consistent

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REACH

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Parting Thoughts

- In the very near future, nanomaterials will be regulated and it is reasonable to assume that some nanomaterials will be hazardous to humans or the environment and litigation will ensue
- Mitigating your exposure risk now makes good business sense

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Thank you!

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