ENVIRONMENTAL DEFENSE
finding the ways that work

Environmental Defense comments on:

Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR)

"Opinion on the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials," dated 29 March 2007

Submitted by
Richard A. Denison, Ph.D., Senior Scientist
Cal Baier-Anderson, Ph.D., Health Scientist

22 May 2007

Key Issue

Overall, we believe this Opinion provides an excellent and comprehensive evaluation of the challenges associated with applying current risk assessment methodologies to manufactured nanomaterials.

In addition to the specific comments offered below, we do have one major overarching concern about this Opinion: its unwarranted and, we believe, ill-advised reliance on exposure-driven decision frameworks, evident in both the Exposure Assessment Algorithm presented on page 15 and the Outline of a staged approach to identifying the human and environmental risks from nanoparticles presented on pages 54-55.

The Opinion does an excellent job of laying out the very substantial data gaps and uncertainties surrounding our understanding of – and the present limitations to our ability to better understand – the nature and extent of exposures to nanoparticles. It repeatedly and appropriately emphasizes the dynamic nature of nanomaterial properties and their potential – largely unstudied to date – to change over time, depending on local environmental conditions, in response to environmental forces (e.g., weathering, degradation, dissolution, etc.), or across the stages of the lifecycle. The Opinion also prominently notes the present difficulties in gaining an understanding of whether a nanomaterial is persistent or has the potential to bioaccumulate – key determinants of exposure potential. Serious technical limitations are described with respect to our ability to measure and monitor for nanomaterials in a variety of settings (workplaces, environmental media, within the human body and other organisms, etc.), and the Opinion also notes the absence of instruments and protocols for conducting exposure monitoring in all of these settings. The lack of validated models to estimate exposures to nanomaterials is discussed as well. Finally, attention is drawn to the critical need to revisit and significantly revise the dose metrics and emission factors used for conventional substances to determine how they may be applied to nanomaterials.

We fully agree with these aspects of the Opinion and believe they represent critical gaps that need to be addressed as soon as possible. Unfortunately, in formulating its Exposure Assessment Algorithm (p. 15) and its Staged Approach (pp. 54-55), the Opinion appears to wholly ignore the very deficiencies it has so thoroughly described. Both of these decision frameworks are based on a clearly faulty assumption that sound determinations about exposure potential can be made *at the outset* of an assessment – and without conducting any serious scientific investigation into the actual or potential extent of exposure. Each decision framework begins by posing simple yes/no questions, the answers to which will be – at best – pure conjecture, given how limited our present ability is to predict exposure to nanomaterials. At worst, using such questions as the key, if not sole, driver as to whether an assessment is needed invites overly simplistic responses or even abuse. This exclusive focus on exposure also departs from the broader approach taken in conventional risk assessment, which requires both the characterization of toxicity (hazard) and exposure as separate components of the assessment that are combined in the risk characterization.

The entry-point questions for each of these decision frameworks use words that are undefined and ambiguous, and no standard of evidence is provided as to how much (if any) empirical information is needed to answer them. The question as to whether the material is "fully contained" begs the further question as to what is meant by *full* containment, especially across the lifecycle of a material. And the question as to whether exposure is "likely" is even more subjective – especially when the assertion is made (on p. 56) that it can be answered merely by conducting a "desk top evaluation of the lifecycle of the material."

Experience with a host of conventional chemicals should have taught us that relying on assumptions, even those said to be based on expert judgment, about conditions under which exposure is expected to be low or non-existent are all too frequently proven wrong upon more careful examination. One common mantra – already being repeated in the context of nanomaterials – is that a substance will be fully contained simply because it is "embedded in a matrix." This simplistic view must be rejected outright as insufficient: As just one of a growing list of examples, witness the now-ubiquitous exposure to brominated flame retardants embedded in the polymer matrices that house personal computers and monitors, including their presence in household dusts. Another common mantra – that nanoparticles will invariably agglomerate in the environment and hence not be available to cause exposure to their nano form – is already being called seriously into question. Recent studies with carbon nanotubes (CNTs) have found that humic matter present in natural river water can act to stabilize individual CNTs so that they remain dispersed as single particles.[1] Moreover, researchers are working hard to render nanoparticles that tend to clump more dispersible, e.g., through surface modifications or treatments, in order to enhance the ability to more evenly disperse them in application so as to enhance performance; such modified materials may well also remain more dispersed if released to ambient air or water.

Recent history should impart a substantial degree of humility regarding our ability to predict exposure based on first principles. Perfluorinated chemicals used as water, stain and grease repellants on everything from textiles to food packaging to cookware are now detected in virtually all humans on earth – and got there by means we have yet to understand. Mounting evidence of releases of and exposures to chemicals such as phthalate esters and bisphenol A that

[1] Hyung H, Fortner J, Hughes JB, and J Hong Kim. 2007. "Natural Organic Matter Stabilizes Carbon Nanotubes in the Aqueous Phase." *Environ Sci Technol*. 41(1); 179-184.

were initially claimed to be impossible or unlikely should likewise serve to turn simplistic assumptions about exposure potential on their heads.

This speculation-about-exposure approach has three additional major problems. First, it is far from precautionary, which given the major uncertainties involved should certainly be the approach taken. The text accompanying these figures is actually better-worded: On page 16 under Step 1, the standard that must be met to forgo further assessment is that exposure at each stage of the lifecycle is found to be "highly unlikely" – far more rigorous a standard than that used in the diagram on p. 15 and in the boldfaced Step 1 heading itself, which merely asks for speculation as to whether exposure is "likely." Similarly, the text on p. 53 describing Stage 1 requires determining whether exposure "could result," again a more cautionary standard to be met than determining whether exposure is "likely." At the very least, these questions should be reworded to reflect a more precautionary approach, and some discussion of what degree of actual investigation and scientific assessment is needed to meet the evidentiary standard should be provided.

Second, while the Opinion itself appropriately emphasizes the potential for nanomaterials to change their properties, including across the lifecycle, in ways that can affect their exposure potential as well as hazard properties, the decision algorithms either fail to ask such questions or do so only well after the initial yes/no questions are answered. These lifecycle aspects of exposure potential need to be considered at the outset.

Finally, and most problematic, is the fact that reliance on the decision frameworks will at best postpone and may well preclude altogether ANY development of even the most basic information regarding a nonmaterial's hazard. While exposure considerations may well be relevant in deciding which types of and how much hazard testing is needed, ***the two evaluations of hazard and exposure need to be pursued in parallel***. This is true not only because there is enormous uncertainty associated in predicting actual exposure, given the novel properties and behavior of nanomaterials. Developing some understanding of hazard starting early in the assessment process is also essential because deciding whether or not exposure is in fact "low" requires knowing something about how toxic the material in question actually is, and how it behaves within an organism (does it accumulate? if so, where? etc.).

The Opinion itself appears to acknowledge this limitation to solely exposure-driven approaches being applied to nanomaterials, at the top of page 57: "In principle, a generic exposure level should be identifiable that is gauged as too low to be of concern, similar to general thresholds of toxicological concern discussed by Kroes et al, 2004. However, there is no information as to whether this is applicable to the assessment of manufactured nanoparticles and safe levels cannot currently be identified on this basis."

As a final consideration, it simply must be acknowledged that use of a purely exposure-driven approach could well undermine our ability to develop a good understanding of nanomaterials' risks – which, of course, are functions of both hazard and exposure – because there are other strong disincentives to conducting hazard testing. Especially where such a decision framework is to be applied by industry, a major motivation exists to assume low exposure if that means that the costs of conducting hazard testing can be avoided. In the case of application by government, cost avoidance as well as animal welfare concerns are also motivating factors. This is ***not*** to say that minimizing cost and unnecessary animal use are not worthy objectives; rather, those

objectives must be balanced against the essential need to identify and mitigate any risks to humans, animals and the rest of the environment.

For all of these reasons, we urge SCENIHR to reformulate its decision frameworks so as to put far more emphasis on the need to develop a basic understanding of hazard as well as exposure potential from the outset. One model for such an approach, in the development of which we have been directly involved, is the DuPont-Environmental Defense Nano Risk Framework (see www.nanoriskframework.org), which calls for the parallel development of basic profiles for both hazard and exposure of a nanomaterial.

For the exposure track of a parallel approach, the use of a lifecycle framework to anchor the assessment is entirely appropriate. The first step should be a thorough and systematic cataloguing of the processes and activities involving a substance at each stage of the lifecycle. This method should be applied to both known and all reasonably anticipated lifecycles. Such a catalog can then serve several purposes. It can bring focus to questions about potential exposures to or releases of a material. It can also make more concrete the need to consider what changes in the material's physical form and properties may have occurred at each step that could affect its release or exposure potential and hence need to be evaluated. Finally, each such point of potential release or exposure should be the point of departure for further rigorous analysis of the subsequent fate and behavior of the material, including its potential for transformation by physical, environmental or biological means.

Specific Comments

Page 13, 3.1: "Phenomena such as dissolution, agglomeration and coalescence have to be taken into account …." This is the first of many mentions of the potential for nanomaterials to agglomerate; equal attention must be paid to the potential for them to ***de-agglomerate***; see discussion of this issue and literature reference cited earlier.

Page 14, 3.2.2: We strongly support the emphasis here on the potential for nanomaterial characteristics to change over the lifecycle of the material.

Page 14, 3.3.1: "In order to measure exposure to manufactured nanoparticles, it is necessary to take into account the background exposure to ambient nanoparticles such as combustion derived nanoparticles." Two rationales are perhaps intended by this statement but should be explicitly stated. First, the presence of background nanoparticles may make it more difficult to *detect* manufactured nanoparticles above the background. Second, the presence of background nanoparticles may result in or lead to similar exposures and/or types of effects, such that the contribution of the manufactured nanoparticles may not be readily discerned.

Page 15: See our earlier comments regarding the exposure assessment algorithm.

Regarding "soluble particles:" Solubility in biological fluids must be considered, including the scenario whereby a water-insoluble particle enters an organism (e.g., the lung interstitium) and there becomes soluble (e.g., in lung surfactant), releasing its constituents in a location in which the dissolved constituents would not otherwise have ever reached. This scenario is entirely analogous to the legitimate concern raised in the Opinion that nanoparticles may serve as "carriers" of other toxic substances.

Page 16, 3.3.1.2, explanation of Step 2: This discussion appears to ignore the potential for the substance to be delivered to a location, due to it being in nano form, where it can exert novel toxicity because of where it resides, not because it is composed a novel substance.

Page 17, 3.3.1.2, explanation of Step 6: First, there is an apparent assumption that agglomerated nanoparticles will be equivalent in activity, including toxicity, to a microscale particle of the bulk material. Many agglomerated nanomaterials retain much of their "nano-ness" due, e.g., to only slight reductions in surface area as a result of agglomeration. Second, the potential for de-agglomeration, needs to be considered. Third, the answer to this question may well depend on and vary based on specific settings or conditions, so the question must be considered for each of the many possible settings, including across the lifecycle, in which the nanomaterial may be present.

Page 17, 3.3.1.2, explanation of Step 8: " … the final considerations from an exposure viewpoint are the nature and the extent of the ***toxic response*** to the free nanoparticles compared with those of larger particles of the same chemical(s). If the nanoparticle form of the product of interest constitutes a substantially higher ***risk***, or is substantially different in nature, compared to that of larger particles, a full assessment of exposure of humans and/or environmental species is likely to be necessary." This step could only be carried out if substantial information about the nonmaterial's toxicity were already known. This is why, in our introductory comments above, we emphasize the need to develop both hazard and exposure-relevant data in parallel.

Page 18: Any assumptions that containment and personal protective equipment are effective methods of controlling exposures need to be empirically tested, little of which has been done to date. The statements here tend to state such assumptions as fact.

Page 19, 3.3.3: "The release or redispersion of free nanoparticles that are embedded in solid matrices of various nanotechnology products seems unlikely during the break-down." This assumption may well not be the case: the breakdown of vehicle tires through wear during use can contribute to the amounts of respirable particles near roads, and such particles contain constituent materials from the tire. Erosion of coatings (e.g., paints) can yield very small respirable particles containing constituents of the coating, shown most dramatically in the contribution of lead to respirable household dust from paint applied to interior walls as it ages. While such particles may not necessarily be at the nanoscale, it may hardly matter with respect to their potential to lead to exposure to the original nanoscale component.

Page 21: Translocation may not be based on size alone; composition, surface charge, etc. may also be important.

Page 23, 3.4.3.3: People with hypertension represent a very large sensitive subpopulation, which, given the findings reported here, may well warrant special attention in any risk assessment. The reference provided on the ability of nanoparticles to cross the blood brain barrier pertains to a drug delivery study (Lockman 2004) in which the nanomaterials were developed for this purpose. This should be noted lest the impression be left that all nanomaterials necessarily are able to cross such barriers (also found on page 51).

Page 28, 3.6: "Accordingly, the particle characteristics should be measured under conditions that mimic those of the intended use." Use may not be the only phase during which exposure could

occur. It would be better to say that particle characteristics be measured under conditions that mimic any and all relevant potential exposure settings.

Page 34, 4.1.2.1, boldfaced text: De-agglomeration as well as agglomeration potential needs to be noted here, for the reasons discussed earlier.

Page 38, 4.1.3.1: The discussion of the limitations of QSARs, while important, is too limited: QSARs for nanomaterials, unlike those for conventional chemicals, would have to account for more than just ***molecular structure***, because their properties are dictated by physical as well as chemical structural characteristics and properties. It follows that predicting activity of a nanomaterial using a QSAR would have to involve knowing more than just its molecular structure.

Page 54, Stage 2, The Form of Exposure: The discussion of rapid agglomeration is far too simplistic. Under what conditions? Might there also be de-agglomeration under subsequent conditions the material encounters? Note the discussion and reference we provided in our earlier comments: clumped CNTs became individually dispersed when brought into contact with river water.

Page 57, Step c: Here and in a few other places in this section, reference is made to knowledge about physical-chemical properties of a nanomaterial, presuming such knowledge to already exist. Yet the schematic on pp. 54-55 does not include any step by which such information would be generated. This is a serious omission.

Page 58, Step c: The discussion here of the ability to rely exclusively or nearly so on results from in vitro tests assumes that such tests have been developed for nanomaterials, and found to be valid, including that they serve as reasonable replacements for in vivo tests – that is, the results found in vitro correlate with those found in vivo. None of these assumptions is warranted at the present time, however desirable such a situation would be. The only way this will arise is if sufficient empirical data from parallel in vivo and in vitro testing of the same nanomaterials are developed to allow for such correlations to be established. More hopeful at this time is for the use of in vitro tests to complement in vivo information, rather than serve as a replacement for it. As the Opinion elegantly points out on page 30, these two types of provide different but complementary information.

We appreciate the opportunity to offer and your consideration of these comments. [END]