The Nanotechnology Panel of the American Chemistry Council Comments in the Public Internet Consultation of the Commission (DG Health & Consumer Protection) on the Scientific Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on the Technical Guidance Documents of the chemicals legislation, for the risk assessment of nanomaterials

Submitted 23 May 2007

General Comments:

The Commission has been asked to review the Technical Guidance documents with respect to their use for the risk assessment of nanoscale materials. Ultimately, any identified risks must be managed and it should be noted that even in the absence of detailed information of the hazards and exposures that in combination make up risk it is possible to perform effective Risk Management. Effective Risk Management can be achieved by taking sufficiently conservative actions that minimize exposure such as through the use of engineering controls, personal protective equipment, and control of releases of materials. The information that will be obtained about the hazards and exposures may ultimately show that a reduced degree of rigor is needed to provide effective Risk Management than used initially.

Risk Assessment requires a good understanding of the material being evaluated (Characterization), the possible effects on people and the environment (Hazards) and how it is used (Exposure). The Technical Guidance documents and the SCENIHR review focus primarily on the hazard assessment and secondarily on the exposure. An increased focus on characterization is needed.

Physical Chemistry and Characterization Comments:

The Nanotechnology Panel (Panel) agrees that, in general, existing risk assessment methodologies can be used to characterize and guide the management of the health and environmental risks of nanoparticles. In any assessment of risk it is essential to recognize the two factors that determine the overall risk – hazard and exposure. In order to interpret the exposure component of dose/response relationships, the Panel agrees that it will be important to characterize thoroughly test materials both in their bulk form and in the context of experimental exposure media and to establish clearly the relevance of the experimental exposure to the risk assessment scenario. Additionally, the Panel agrees that because mass concentration may not be an appropriate description of dose for nanoparticles, it will be important to continue to explore various dose metrics (surface area, particle number, weight) in order to fully understand the best dose metric(s) for characterization of dose/effect and dose response relationships.

It is likely that many of the existing methods used for the hazard evaluation of non-nanoscale materials will also be sufficient for nanoscale forms. It is important to understand the basis for each method and to establish relevant dosimetry. This understanding should then be considered to determine if particle size is an important factor in dosimetry and if adjustments to the method need be made to achieve relevant dosimetry. For example, if the nanoscale test substance is not available at the molecular level due to lack of solubility, aggregation, agglomeration, etc., then size may matter, and the selected test needs to be evaluated to determine if it is still capable of assessing the target hazard.

It has been noted that nanoscale particles have a larger surface area to mass ratio. This may result in greater sensitivity of a test method to the reactivity of a surface, and this aspect should be considered when performing a hazard determination. The effect of surface contamination may be magnified so that the determined hazard may not be due to the nanoparticle but rather due to contamination of the nanoparticle surface. Contamination may also affect other particle characteristics, such as, mobility, which is an important consideration for movement of nanoparticles in and out of cells, within cells, within organisms (translocation), and between environmental compartments.

Human Health Comments:

The Panel agrees that current methods should generally be acceptable for characterizing the potential risks associated with nanoparticle exposure and that not all nanoparticle formulations have been found to induce a more pronounced toxicity than the bulk formulations of the same substances. The statement in section 3.3.1.2 (step 2) discounts the value of information generated on bulk materials. While we agree that information on bulk material alone many not be sufficient to evaluate the nanoparticle form, such information has value in assessing hazard. A particle that is a sensitizer in its bulk form will still be a sensitizer in its nano form. This information helps focus the studies necessary to evaluate nanomaterials.

The Panel also agrees it is important to identify factors associated with nanoparticles that add uncertainty/complexity to assessing risk. To avoid unnecessary testing, it is critical to distinguish those factors that are unique to nanoparticles from those that are equally relevant to other types of xenobiotics. For example, the SCENIHR document emphasizes reasons why new techniques are needed for the elucidation of potential hazard associated with nanoparticles when many of the factors cited are equally relevant to other types of xenobiotics. The discussion regarding addresses factors that have been mentioned in the context of nanoparticles that the Panel feels are relevant to risk assessment in general and are adequately addressed with existing methods.

ADME

While the document claims that the modes of uptake, translocation and mechanisms of toxicity are largely unknown for nanoparticulates, the same could be said for many new chemical entities prior to their study. The Panel nonetheless concurs that study of the disposition of nanoparticle materials will add important information needed for risk assessment purposes.

Mechanisms of Nanoparticle Toxicity

The full text of the document discusses use of in vitro tests in the context of defining mechanism of action. Generally these types of in vitro tests are not "validated" as a replacement for in vivo studies. Instead, in vitro tests designed to elucidate mechanism of action may be specifically tailored to a given chemical (or particle) to test specific hypotheses generated from in vivo observations and hence do not lend themselves to "validation". Instead of formal validation, these tests would need to be scrutinized on a case-by-case basis for biological plausibility in the context of the in vivo data.

Other

Risk assessment for genotoxicity of nanoparticles, including extrapolation from in vitro tests to the in vivo situation, should be handled with the same cautions as risk assessments of standard particles/materials.

The Panel questions SCENIHR's statement that inhalation study designs necessarily need "improvement" for the study of nanoparticles. Careful evaluation of dose/response/time sequences and effects should reveal the impact of inhibition of clearance via discontinuity of the dose response curves. These same types of issues have been important in understanding the effects of larger particles. Although the dose response curves may potentially be different, the same principles, particularly related to high to low dose extrapolation, apply.

Similarly, it is not clear why new methods are needed for the examination of neurotoxicity. Current methods that evaluate structure and function would be anticipated to be sufficient to reveal any underlying toxicity.

We **disagree** with the view that assays for the monitoring of blood and brain transfer of nanoparticles and their consequences, have to be developed. Specifically, there is no available evidence that current toxicokinetic methods would fail to detect the presence/absence of nanoparticles in nervous tissue.

Environmental Comments:

The SCENIHR document provides an excellent review of the topics relevant to environmental fate and effects of nanoparticles and notes that the prediction of environmental concentrations by conventional means will be difficult.

Based on these and other findings, the Committee believes that a full quantitative risk assessment is not presently possible for nanoparticles due to the inability to estimate the PECs and PNECs with confidence. We agree with this view. However, we **disagree** with the Committee's statement that there is necessarily a need for new standardized tests as refinement of existing tests may be sufficient taking into account characterization data and improvements in analytical capabilities.

The overall assessment may be improved through the addition of clarifying statements that indicate the importance of understanding the relationship between exposure in the context of human or environmental risk assessment scenarios and exposure (dosimetry) in the context of methods used to evaluate the potential hazards. Clarifying statements should also be added regarding contamination of nanoparticle surfaces. The Panel generally agrees with the statements made with respect to Question 1 but believes that the overall risk assessment will be improved by addressing the comments provided above.

In general, the Panel agrees with the statements made with respect to Question 2. The importance of the determination of hazards should be made very clear since this knowledge is essential for a sound assessment of risk. Nanoscale materials may have different physical properties than their larger counterparts that may result in different biological/toxicological properties. While this may be true it is also possible that changes in physical properties may not result in any qualitative or quantitative differences in toxicity.

As with hazard and risk assessment for other types of materials, it is possible to identify hazards and conduct risk assessments based on conservative assumptions and with extensive compound (particle) specific data. Ultimately, further elucidation of the mechanism of action of nanoparticulates, particularly in the context of specific factors that may drive divergence in toxicity between nanoparticulates and larger particles, will facilitate refinement of risk assessments and the development of rules for read across between various nanoparticulates and their corresponding larger particle forms. Elucidation of this mechanism along with an understanding of the role of particle dosimetry in driving any noted particle size specific effects will facilitate the development and validation of in vitro screening and ranking models. An improved understanding of mechanisms will ultimately lead to an improved ability to build models from which more accurate hazard assessments may be obtained.

The Panel **disagrees** with the statement "Similarly, since there is some evidence that nanoparticles can translocate from the lungs to the blood and the brain, assays for the monitoring of blood and brain transfer of nanoparticles, and their consequences, **have to be developed.** For blood, markers of thrombosis and atherogenesis need to be considered and **potential degenerative effects and oxidative stress on the brain should be assessed within these new methods."**

The Panel believes that current test methods are sufficiently robust to detect translocation of nanoparticles from blood to the brain and that the suggestion above is

unwarranted. The Panel agrees that knowing solubility of the nanoparticle in an aqueous media is the key to understanding particle biodurability. A complicating factor in the interpretation of in vitro tests with nanomaterials is dosimetry. There may be confounding factors that make the relationships between human exposure, applied dose in the culture system, and internal dose to the cells more complex than for other materials. This is appropriately highlighted in sections such as on genetic toxicology.

The overall assessment may be improved through the addition of clarifying statements to support a thorough understanding of existing test methods and the materials to be evaluated. Subsequent efforts should focus on building mechanistic and dosimetry relationship information to both refine risk assessments and develop in vitro screening and ranking tools. The Panel mostly agrees with the statements made with respect to Question 2 but feels that the overall risk assessment will be improved by addressing the comments provided above.

The Panel supports the use of a tiered assessment program for risk assessment. As already noted, characterization of test materials and understanding relevant dosimetry are essential for performing a sound risk assessment. It is practical for an assessment to be conducted in a step-wise manner so that evaluations build on new knowledge and/or if the assessment shows negligible risk at any step of the process, the evaluation can be closed and resources then used to investigate other materials for which the risks are not yet clear.

The overall assessment could be improved by the addition of clarifying statements to make clear the importance of the characterization of the test substance to ensure that the material and its nanoscale form that is the intended subject of the evaluation are actually the material and form evaluated. It must be ensured that the composition, particle size, impurities, surface contaminants, etc. be determined so the influence of such factors on any observed effects may be investigated and understood more fully. The Panel generally agrees with the statements made with respect to Question 3, but believes that the overall risk assessment will be improved by addressing the comments provided above.