Review of the 29 March 2007 SCENIHR Opinion on
The appropriateness of the risk assessment methodology in accordance with the TGD for new and existing substances for assessing the risks of nanomaterials

- 22 May 2007 -

1. General comments

- Overall, the consultation document is thorough and generally balanced in tone. Exceptions are identified in specific comments, below. Organization could be tightened up considerably, as the same comments appear in multiple parts of the document.
- The recognition that nanomaterials should not be treated as a class of materials, but instead be "evaluated on a case by case basis," appears to be supported by the toxicity data in the scientific literature.
- Considering the wide range of nanoparticles to be assessed, agreed reference nanomaterials can be valuable, although probably difficult to characterize, in evaluating differences likely to exist between monomeric versus polymeric and organic versus inorganic nanoparticles and their macro sized counterparts.

2. Exposure Control Measures:

- The document states that the main method used for controlling nanoparticles, such as TiO_2, during production are under total containment or a closed system. This is not universally adopted in industry.
- There is no national or international consensus on measurement techniques or standards for monitoring nanoparticles in the workplace, and no standard definition of what a nanoparticle is. These should be developed.
- There is the need for a measurement device that can differentiate between engineered nanoparticles and the background level of natural.

3. Risk Assessment Methodology

- Stability of nanoparticles and the long-term effects on, for example, the unborn, the elderly, and in different environmental compartments urgently need to be assessed.
- Biological processes involving nanoparticles, including translocation, cellular uptake and toxicologic mechanism are still largely unknown and may differ depending on particle type and the surface layer.
- In order to avoid the hindering of innovation, the development of appropriate tools to deal with risks related to nanotechnologies, investments are required in focused research.

Place des Maïeurs, 2 • B-1150 Brussels, Belgium • Tel.: +32 2 772 22 12 – Fax: +32 2 771 39 09 •
V.A.T.: BE 423.939.488 e-mail: eucomed@eucomed.be • www.eucomed.org

4. Toxicology Testing

- There are many different attributes of nanoparticles that may influence their human toxicological and ecotoxicological properties. Whole organism (*in vivo*) studies are a way of integrating all potential effects, as compared to in vitro studies that may be better suited to identifying mechanisms.
- Nanoparticles have complex physiochemical properties that can modulate their biological activity. There are considerable mechanistic and dose discrepancies that exist between *in vitro, in vivo and ex vivo* testing, and even between different routes of exposure *in vivo* in test species.
- Existing toxicology toolbox may not be adequate for assessing the effect of the physicochemical properties of nanoparticles.

5. Worker exposure

- Emerging research indicates existing respiratory protection techniques (e.g., use of HEPA filters) may be effective in removing nanoparticles.
- There are a number of uncertainties when extrapolating from animal results to humans when it comes to inhalation exposure; therefore, evaluation of nanoparticles is advocated on a case-by-case basis.
- The potential for dermal penetration is largely unknown for most nanomaterials.

6. Environmental effects

- Development of "base set" aquatic toxicity data on a range of reference nanomaterials would be informative and could be compared to similar data on macromaterials.
- Development of standard exposure scenarios for commonly used nanoparticles would facilitate the risk assessment of nanomaterials.

Specific Comments (first occurrence cited; however, many topics appear throughout the document in multiple locations).

Abstract, 2nd paragraph, lines 11-13: The key point, "evaluation of nanoparticle formulations should be carried out on a case by case basis," is deemphasized in the rest of the document, which focuses on potential adverse effects. Indeed, the point is lost two paragraphs later! See next comment.

Abstract, 4th paragraph, lines 4-5: The need for new ecotoxicity tests doesn't appear to be supported by newly emerging aquatic toxicity data (e.g., see SETAC abstracts for the 2006 and 2007 annual meetings in Europe and North America). However, it is agreed that additional organisms representing additional taxa may have to be tested with a series of standard reference nanoparticles to rule out unforeseen effects on specific trophic levels not commonly assessed under the TGD.

EXSUM, page 8, paragraphs 3 and 4: Taken together, these paragraphs highlight the uncertainty surrounding the adequacy of existing modeling and testing protocols (presumable pertaining to dosing or exposure of test organisms?). The call to develop scenarios reflecting actual production and use is problematic given the variety of nanomaterials and the different production processes and end uses. This combination of factors lends further credence to "evaluation of nanoparticle formulations should be carried out on a case by case basis." Taken to the extreme, it could be construed to suggest that chronic testing is necessary to ascertain potential ecotoxicity risks.

EXSUM, page 8, paragraph 5: Contradictory data exist on which is the most appropriate dose metric with some reports indicating surface area or particle number is more appropriate, while other data indicate no difference between particle mass and surface area (see recent publications on studies of nano and micro TiO2 by Warheit, DuPont Haskel Laboratory). This further points to the near-term need that the traditional use of mass or mass per unit volume may be appropriate in certain circumstances. However for other nano particles alternative dose metrics may be appropriate. "Evaluation of nanoparticle formulations should be carried out on a case by case basis," and should have to be considered when running the PEC:PNEC evaluation since units will have to be consistent.

EXSUM, page 9, paragraph 6: We agree that appropriate reference materials should be identified and tested via standardized protocols. As a start, existing OECD guideline studies (i.e., "base set" testing) should be considered with careful attention paid to exposure of the organisms to the nanoparticles.

EXSUM, page 9, paragraph 8: Interpretation of genotoxicity, carcinogenicity, irritation and sensitization of nanoparticles is of particular importance. The extrapolation of genotoxicity data and other relevant toxicity data from macromaterials to nanoparticles needs to be approached with caution.

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EXSUM, page 9, paragraph 9: Determination of bioavailability *may* require testing in different taxa than those routinely used.

Pg 14, section 3.3.1, line 4: Regarding "manufactured nanoparticles," much information is available on welding fumes, which may have some relevance to assessing potential effects of nanoparticles.

Pg 14, section 3.3.1, line 7: Assumption is made that the number of particles is more critical than the mass. Consensus does not exist on this point.

Pg. 16, section 3.3.1.2, Step 1, line 1: "An evaluation" is vague. A more descriptive process on how to conduct an evaluation and what to look for when dealing with nanoparticles is needed.

Pg. 17, section 3.3.1.3, line 8: Appropriate monitoring methods for conducting personal exposure assessments still need to be defined. Current industrial hygiene personal air sampling methods are not adequate. In order to measure number versus mass, a different technique is required.

Pg. 18, section 3.3.1.3, line 5: The availability of "simple techniques" is limited. For example, a cascade impactor is a device that would allow for separation and collection of several particle sizes. These devices, however, are not proven for monitoring personal employee exposures to nanomaterials.

Pg 18, section 3.3.2.2, line 5: It is essential that the entry hood is always positioned correctly and adequate capture velocity is maintained. Consider the requirement of performance testing of laboratory fume hood, i.e. ASHRAE 110 or EN14175.

Pg 19, section 3.3.3, 3rd paragraph, last line: This point would support development of chronic aquatic toxicity data for a set of well characterized reference materials, and would inform the approach to PBT assessment.

Pg 26, section 3.4.4, 3rd paragraph: The effects of solvent (THF) has been further evaluated in zebrafish larvae by Henry et al. (in press, Env Health Perspectives), who attributed observed toxicity to THF degradation products and not to the nano material, C60.

Pg 27, section 3.5.2, 2nd paragraph: There are different human exposure scenarios during the different stages of the life cycle of nanomaterials during production, processing and distribution, use and application, storage, and waste disposal or recycling. These should be addressed through development of standardized exposure scenarios for representative product uses and nanomaterials.

Pg 29, section 3.6.2, 2nd paragraphs: .Dose metrics deserve additional discussion than what is provided. While respirable mass fraction does not provide direct information on other dose metrics, such as the number or surface area of particles that may be more relevant measures for certain nanoparticle health effects, it remains a valid, reproducible metric for evaluating "dose."

Pg 29, section 3.6.2, 5th paragraph: It is stated that for some nanoparticles, health effects correlate best with the surface area measured by the BET nitrogen absorption methodology. This statement appears to be in relation to the findings of epidemiology studies of air pollution effects on humans and may not be universally applicable to other types of nanoparticles.

Pg 40, section 4.1.3.4, 1st paragraph: This is not universal across the various types of nanomaterials. For example, the acute toxicity to fish from exposure to nano-TiO_2 (unpublished data provided to DG-Sanco) is no different from what has been reported in the literature for macrosized material. Separate triggers for nanomaterials have to be specified on type of material, not because it is "nano."

Pg 45, section 4.2.1, 1st full paragraph: The acknowledgement that chemical and physical processes in the environmental compartments may cause the number of particles and resulting surface area characteristics to change (e.g., agglomeration; aging), and therefore the dose-response for effects, would support development of chronic aquatic toxicity data for a set of reference materials, and would also inform the approach to PBT assessment (see Section 4.2.3).

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