

NIA Comment on

The public consultation on

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the European Commission (EC) Opinion, approved on 29th March 2007:

Appropriateness of the EU Technical Guidance Documents (TGD) of chemical legislation for nanomaterials

May 2007

Introduction to the NIA

Formed in 2005, the Nanotechnology Industries Association (NIA) creates a clear single voice to represent the diverse industries' views in the multi-stakeholder debate on nanotechnology, by providing an interface with government, acting as a source for consultation on regulation and standards, communicating the benefits of nanotechnologies and interacting with the media to ensure an ongoing advancement and commercialisation of nanotechnologies.

The unique feature of the NIA is that it provides a purely industry-led perspective derived from the views of the collective membership, which is made up of many varied companies all at different stages of their life cycle and with a variety of interests in the huge range of technologies that derive their benefit from the nanoscale. This enables those seeking comment from industry to have a single point of entry to the industry and avoids the need to approach individual companies for statements on specific issues. In addition the breadth of the membership enables the NIA to put forward strong proposals to government and regulatory authorities to promote an environment that supports the application and utilisation of nanotechnologies. Initial aims of the association are:

- promoting the responsible use of nanotechnology and raising awareness of its many applications in an unbiased way among key audiences within the UK,
- generating position statements and papers in areas relevant to its members and providing responses to consultations exercises,
- technology foresight exercises examining current products, developments and future applications of nanotechnologies with an industry-based perspective on the risk-based classification of emerging technologies including nanotechnology, which is linked to a new hazard assessment methodology as the current project,
- working closely with regulators to represent the interests of the NIA to ensure the future of nanotechnology is secured and to realise its full potential,
- encouraging and stimulating industry participation and support for nanotechnology, and
- providing a forum for discussing topics of relevance to its members.

For further information visit <http://www.nanotechia.co.uk>.

1. General Comments

Overall, the consultation document is thorough and generally balanced in tone; exceptions are identified in specific comments, below. The overall organisation, however, 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 in evaluating differences likely to exist between monomeric *versus* polymeric and organic *versus* inorganic nanoparticles.

2. Exposure Control Measures

The document states that the main method used for controlling nanoparticles, such as TiO₂, during production are '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, or equivalent definitions adopted (e.g. the ISO/TC 229 definition, now adopted by the OECD WPMN).

There is a strong need for a measurement device that can differentiate between engineered nanoparticles and the background level of natural.

3. Risk Assessment Methodology

Long-term stability of nanoparticles needs to be assessed; effects on the unborn, the elderly, and in different environmental compartments are still unknown.

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.

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 may have complex physiochemical prosperities that can modulate their biological activity. There are considerable mechanistic and dose discrepancies that exist between *in vitro* and *in vivo* testing, and even between different routes of exposure *in vivo* in test species.

5. Worker exposure

Emerging research indicates existing respiratory protection techniques (e.g. use of HEPA filters) are effective in remove 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 deemphasised 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 prejudgment of the need for new ecotoxicity tests isn't justified and 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). Furthermore, this appears to be contrary to the statement in paragraph 3 of the Executive Summary. However, it is agreed that additional organisms representing additional taxa may have to be tested with a series of standard test 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 (presumably 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: We disagree with the general statement that "the traditional use of mass or mass per unit volume alone is unlikely to be appropriate." 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 furthermore points to the near-term need that "evaluation of nanoparticle formulations should be carried out on a case-by-case basis," and will also have a direct impact on 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* standardised 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.

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 IH 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 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 nanomaterial, 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 standardised 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-TiO₂ (unpublished data provided to DG-Sanco) is no different from what has been reported in the literature for macrosised 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 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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