

NIA Comments

on
**Scientific Committee on Emerging and Newly Identified
Health Risks (SCENIHR)
Opinion on
*Risk Assessment of Products of Nanotechnologies***

The NIA, Nanotechnology Industries Association (NIA), is the market-independent, responsible voice for the industrial nanotechnologies supply chains; it supports the ongoing innovation and commercialisation of the next generation of technologies and promotes their safe and reliable advancement.

The NIA stands for science- and technology-based expertise in nanotechnologies, encompassing members companies that have successfully developed and commercialised nanotechnologies for over 25 years.

Through proactive collaborations with regulators on the national, European and international level, as well as engagement with other nanotechnology stakeholders, the NIA promotes a framework of shared principles for the safe, sustainable and socially supportive development and use of nanotechnologies, by securing a publically and regulatory supportive environment for the continuing advancement and establishment of nanotechnology innovation.

Background

In recognition of the importance of the issue of safety of nanotechnologies, the Commission is organising a one-day scientific hearing, which will take place on 10 September 2009 in Brussels. The hearing will focus on the scientific aspects of the issues covered in the SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) opinions related to Nanotechnology.

In order to prepare for this hearing, the Commission is launching a public consultation with three main objectives:

- *identification of any possible topics which have not been covered in the opinions from the relevant EU Risk Assessment Committees and Bodies;*
- *identification of what are, according to current scientific knowledge, the main potential risks that could emerge from the use of nanomaterials in the future;*
and
- *identification of the issues to be discussed at the hearing, including provision of background information and comments on those issues.*

The outcome of the consultation will be presented at the Scientific Hearing in September.

Comments

In summary, we recommend the following issues to be considered for further focus by the Scientific Committees:

- distinction, description and determination of unique nanoscale effects and properties (as opposed to those that are extrapolations from a larger size, such as surface area dependent reactivity)
- support of technology- and science-based terminologies and definitions agreed by international fora
- coordinated research in the following area needs to be advanced and the resulting findings reviewed:
 - release and fate, and exposures of nanomaterials within the environment
 - transport and fate of primary nanoparticles in biological systems
 - mechanism of toxicological effects caused by nanomaterials in biological systems
 - establishment of reliable and standardised measurement techniques, [...] and implementation of screening/monitoring of nanoscale particles
 - improvement of the understanding of derivatisation and alteration of nanomaterials in the environment.

Risk assessment of nanomaterials:

We agree with SCENIHR on their conclusion that *'[t]he hypothesis that smaller means more reactive and thus more toxic cannot be substantiated by the published data. In this respect nanomaterials are similar to normal substances in that some may be toxic and some may not.'*

We furthermore support the *'case by case approach for the risk assessment of nanomaterials'*, as recommended by SCENIHR.

We agree with the finding that *'[f]or (partially) soluble nanomaterials the toxicity may be governed at least in part by the soluble species released from the nanomaterial.'*

It is important to distinguish the linearly particle size dependent increase of surface area from the unique properties that are observable below a primary particle size of approximately 100 nm only. More research is needed, in order to characterise the transport properties of primary particles in biological systems, determine if agglomerates or aggregates can revert to primary particles in biological systems, and to ultimately shed light on SCENIHR's suggestion that *'[f]or low solubility or a slow release, the particulate nature of the substance may be relevant with regard to tissue distribution and local release of toxic species which should then be considered in the risk assessment of such nanomaterials.'*

Definition:

SCENIHR recommends the introduction of an additional parameter to uniquely describe nanoscale properties by *'extending the current definition based on physical size by the addition of a limit of the specific surface area to be above 60 m²/g of material volume (the value of 60 m²/g corresponds to the specific surface area of*

100 nm solid spheres of unit density) [...]. 'We do not support the addition of a limit of the specific surface area into the unique definition of nanomaterials, since it represents a direct dependence on particle size and contradicts SCENIHR's conclusion that '[t]he hypothesis that smaller means more reactive and thus more toxic cannot be substantiated by the published data.' While we support the notion of a minimum surface area, below which no material shall be considered to be a nanomaterial, we do not support the definition of nanomaterials on one physico-chemical property alone.

Further, the cosmetic industry has worked hard with the EU Commission on the definition laid down in the new regulation on nanomaterials in cosmetics and is preparing notification of nanomaterials to the EU Commission along the lines of the legal definition for regulatory compliance purposes. Any discussion of "definition" should acknowledge the existence of this recent regulatory development.

SCENIHR questions the meaning of the terminology 'nanomaterial', as widely agreed by international fora like the OECD; SCENIHR suggests that *'[d]epending on the nanomaterial, the majority of the particulates may actually be agglomerates/aggregates. This may lead to the misinterpretation that agglomerates/aggregates of nanoparticles that have dimensions well beyond the 100 nm size are not considered nanomaterials. Yet they retain specific physicochemical properties which are characteristic for nanomaterials, most likely due to their relative large specific surface area (SSA).'*

The ISO *'Technical Specification of Nanotechnologies - Terminology and definitions for nano-objects - Nanoparticle, nanofibre and nanoplate'* (ISO TS 27687) does not define the term 'nanomaterial', but it describes the term '*nano-object*' as a '*material with one, two or three external dimensions in the nanoscale*', with '*nanoscale*' being the '*size range from approximately 1 nm to 100 nm [NOTE 1: Properties that are not extrapolations from a larger size will typically, but not exclusively, be exhibited in this size range. For such properties, size limits are considered approximate.]*'. The definition takes into consideration the formation of '*agglomerates*' and '*aggregates*', in which '*nano-objects*' can be '*original source particles*' that '*are termed primary particles*'.

Coordinated research needs:

(a) Risk Assessment

We agree with SCENIHR's findings that *'[m]any of the currently available OECD guidelines for the testing of chemicals are likely to be adequate to detect potential hazards of manufactured nanomaterials as well (SCENIHR 2007a).'* Many of the existing nanomaterials in commercial use have been extensively studied and have been found to present no significant hazard.

SCENIHR writes that *'[t]here is a need for reference nanomaterials since this would allow the assessment of fate and behaviour as well as effects, which could then be related to the material's properties and characteristics.'*

Significant progress on this issue is being achieved by the OECD Working Party on Manufactured Nanomaterials (WPMN), which has agreed the globally coordinated testing of 14 different types of nanomaterials, selected specifically to

address the unique characteristics of manufactured nanomaterials. Industry and regulators are committed to this process by making resources and funding available. A library and repository of the OECD-agreed and other reference nanomaterials is being established by the European Commission as the JRC in ISPRA.

Further coordinated research is required, in order to investigate the transport and fate of primary nanoparticles in biological systems, and to achieve the necessary verification of speculation that suggest *'from the lung and gastrointestinal tract only minimal amounts (approximately 1% or less of the administered dose) enter the systemic circulation. However, although minimal in percentage, this may result in a systemic availability of a considerable number of nanoparticles. The liver and the spleen are the two major organs for distribution. For certain nanoparticles all organs may be at risk as, [...].'*

The large existing history of nanoparticles needs to be reviewed, including carbon black, silica and titania. There is evidence that nanoparticles are everywhere, including cleanrooms. Nanoparticles are created in large volumes in nature. Volcanoes create nanoparticles containing some amount of almost all elements, and in volumes humans will never create. How these have affected life, or how life forms have evolved to handle nanoparticles must be better understood.

(b) Hazard assessment

We agree that further coordinated research is required, in order to investigate the effects of primary nanoparticles on cardiovascular systems; SCENIHR concludes that *'[b]ased on the observations on the effects of particulate matter present in air pollution, some concern exists about the possible effect of manufactured nanoparticles on the cardiovascular system. However, this has not been clearly demonstrated to be the case for manufactured nanoparticles so far. Overall the information on the possible hazard of nanoparticles for cardiovascular effects is rather limited and needs expansion.'*

More attention should be give to investigate the mechanism of toxicological effects of nanomaterials (in particular primary nanoparticles) on biological systems; without conclusive determination of the transport and fate of primary nanoparticles in biological systems, the detection of ROS generation in hazard studies remains on the speculative level. SCENIHR summarises the inconclusive evidence by stating that *'there is some evidence that the small size allows nanoparticles to penetrate into sub-cellular compartments like the mitochondria and the nucleus. The presence of nanomaterials in mitochondria and the nucleus opens the possibility for oxidative stress mediated genotoxicity, and direct interaction with DNA, respectively. For some manufactured nanomaterials genotoxic activity has been reported, mainly associated to ROS generation, while for others contradictory results were obtained.'*

However, all such studies of mechanism of toxicological effects must be conducted using experimental protocols and test systems that have relevance to potential exposure conditions. Walker and Bucher concluded that *'[i]t must be recognized that the specific composition of an in vitro and in vivo test system will likely play a huge role in how a nanomaterial interacts with a cell, or other biological target. This adds a significant complication to the prediction of in vivo health effects'*

from in vitro findings and extrapolation to humans. Agglomeration and aggregation is now recognized as a major issue in both the in vitro and in vivo evaluations of effects of nanomaterials. Depending on the experimental conditions used, the pH, and specific protein content of the environment, methods used to “solubilize” nanomaterials, etc., what was “tested” may often bear little resemblance to the material as it exists in the real world or in a different test system.’ [...] it is also likely that by virtue of their physical attributes and unpredictable and/or artifactual behavior in in vitro systems, the majority of nanomaterials, may not be amenable to study in high throughput assays.’¹

(c) Exposure Assessment:

The OECD WPMN Steering Group 8 on ‘Exposure Measurement and Exposure Mitigation’ published a ‘*Preliminary Analysis of Exposure Measurement and Exposure Mitigation in Occupational Settings: Manufactured Nanomaterials*’.

Based on the analysis of numerous background documents, as well as the incorporation of information gathered in a draft annotated bibliography of exposure mitigation documents prepared by the SG5 (i.e. project on Co-operation on Voluntary Schemes and Regulatory Programmes), the preliminary analysis finds that ‘*[e]ven in the absence of specific exposure limits or guidelines for engineered nanoparticles, exposure measurements can still be used to determine the need for and effectiveness of engineering controls or work practices.*’

SCENIHR takes a rather absolute position in concluding that ‘*differentiation between background and incidental exposure is generally not possible in real life situations as the methods employed mainly measure the presence of (ultrafine) particles and do not discriminate between the different types of particles that may be present.*’

We wish to note that, as part of the OECD Sponsorship Programme, the NIA is leading a consortium, which develops detection and tracking equipment (using isotope tracking) and tests the ecotoxicology and environmental fate of two of the agreed 14 nanomaterials (i.e. ZnO and CeO₂) in detail.² It is anticipated that prototypes of detectors will be developed that allow the isotope tracking of these and other suitable particles in different media. We agree with SCENIHR that ‘*[t]here is a need to further establish reliable and standardised measurement techniques, to develop measurement strategies, and to further implement screening/monitoring of nanoscale particles in sensitive work areas.*’

We agree that more coordinated research is required to improve the understanding of derivatisation and alteration of nanomaterials in the environment; we agree that ‘*[t]he assessment of exposure concentrations of dispersed nanomaterials requires detailed insight into the processes that act on the particles in the environment.*’

¹ Walker, N. J. and Bucher, J. R., ‘A 21st century paradigm for evaluating the health hazards of nanoscale materials?’ Toxicol Sciences, in press 2009.

² For more information on the OECD Sponsorship Programme of Manufactured Nanomaterials, please follow this link: <http://www.nanotechia.org/news/global/oecd-launches-sponsorship-programme-to-test-a-repr>

We particularly welcome SCENIHR's conclusion on the hazard assessment of carbon nanotubes; SCENIHR writes *'[w]hether such nanotubes would pose a risk for humans is unknown, as in addition to these specific nanomaterial characteristics, inhalation exposure to such [i.e. long thin fibrous forms (length >20 micrometer), rigidity, and no degradability (biopersistence)] structures would be essential.'* Upon publication of the Poland *et al.* paper entitled *'Carbon nanotubes introduced into the abdominal cavity display asbestos-like pathogenic behaviour in a pilot study,'*³ the NIA worked with the authors of the paper and the carbon nanotube manufacturers of Europe on a detailed FAQ and full opinion paper. The clarify that the research *'result is not surprising since that is what the research has demonstrated for all fibres studied so far. The Poland et al. study set out to test if nanotubes followed the 'fibre pathogenicity paradigm', which is valid for all fibres including asbestos and glass fibres; it says that fibres are hazardous, if they are stiff and straight, thinner than 3 micrometers and longer than 20 micrometers and biopersistent in the lungs. The study provided some evidence that the CNTs are also following this paradigm; it shows that the CNTs' morphology is an essential factor to their potential to be harmful: two of the four CNTs samples used in the study turned out to display fiber-like pathogenic behaviour whilst the other two did not. The study shows that more research is needed on different nanotubes lengths and on their biopersistence. A structure activity relationship seems possible but needs to be further defined.'*

A recent study helps place the Poland study into perspective and reinforces the importance of fibre length, rather than composition, in producing pathogenic effects; this study evaluated *'the incidence of mesothelioma and other tumors in male Wistar rats injected intraperitoneally with a single dose of MWCNT with defects (2 or 20 mg/animal) and MWCNT without defects (20 mg/animal). Two additional groups of 26 rats were used as positive (2 mg UICC crocidolite /animal) and vehicle controls. After 24 months, while crocidolite induced a clear carcinogenic response (34.6% animals with mesothelioma vs 3.8% in vehicle controls), MWCNT with or without structural defects did not induce mesothelioma in this bioassay (4, 0 or 6%, respectively). The incidence of tumors other than mesothelioma was not significantly increased across the groups.'* One reason discussed for the lack of carcinogenic response was that the length of the MWCNT used in the study was less than 1 μm .⁴

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The NIA and its member companies are grateful for the opportunity to provide these comments.

Brussels, 29th June 2009

³ Poland C, *et al.*, *'Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study'*. Nat Nanotechnol 2008; 3:423-8.

⁴ Muller, J. *et al.*, *'Absence of carcinogenic response to multi-wall carbon nanotubes in a 2-year bioassay in the peritoneal cavity of the rat.'* Toxicol Sciences, in press 2009.