FoEA submission to NICNAS regulatory consultation on

Proposal for Regulatory Reform of Industrial Nanomaterials

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Preliminary comments

Friends of the Earth Australia (FOEA) applauds NICNAS' efforts to develop Australia's first systematic regulation of novel nanomaterials. We also wish to thank NICNAS for its efforts to involve all interested stakeholders and members of the wider public in consultation to develop the regulations. We hope that our submission, along with that of others, will make a useful contribution to this process.

In its Discussion Paper, NICNAS asks for feedback on whether:

- This strategy provides for the sound management of industrial nanomaterials;
- The options meet the needs of all stakeholders to have confidence in the regulatory system through protecting human health and the environment and by providing a clear regulatory path for industry;
- There are other options which could be considered; and
- Any imposts on industry are balanced against the objectives of government and the expectations of the community to ensure public health, worker safety and environmental standards are maintained.

FOEA would like to emphasise that there is not yet enough information available regarding NICNAS' strategy to judge whether or not it provides for the sound management of industrial nanomaterials, or whether it enables confidence in the regulatory system. The Discussion Paper notes that "NICNAS is exploring the feasibility of implementing a more comprehensive regulatory proposal for nano-forms of existing chemicals that addresses triggers identified in the Monash Report" and identifies several desirable features that such a proposal would include. These are promising and FOEA would be interested in participating in further consultation on this. We recognise that regulation of nano-forms of existing chemicals is the most serious challenge, as it involves the overwhelming majority of the nanomaterials used in research and commerce.

Unfortunately, successful regulation of nanomaterials faces considerable challenges and it is not clear how these can be overcome – which is why FOEA continues to call for a moratorium on the commercial use of nanomaterials until the safety science, metrology and measurement work can catch up. Challenes include

- A lack of knowledge regarding nanomaterials' behaviour, biokinetics, biopersistence and risk, how to design reliable risk assessment systems, and how to reliably characterise, measure and detect nanomaterials in products, workplaces and the environment;
- The fact that nanomaterial form, function, bioavailability and risk profile changes significantly throughout the production, handling and manufacture process, through to consumer use and environmental disposal or recycling;
- A lack of regulatory authority, political will and resources to effectively educate manufacturers, importers, handlers, workers and the public to assist them to accurately identify and understand their own use of nanomaterials, to make informed choices and management decisions, and to enforce compliance with new regulations.

The greatest challenges to regulation of nanomaterials therefore lie in the detail of this Strategy's development and implementation, which are not yet available. For this reason, we would like to strongly encourage NICNAS to support a full day face to face consultation with interested stakeholders and members of the public specifically to discuss and further develop the technical detail of its regulatory strategy. This

should take place before the finalisation and release for consultation of the second version of the NICNAS proposed regulatory framework.

The scientific case for a moratorium on the commercial use of nanomaterials

We would like to start by observing although we make this submission and have participated in the NICNAS consultations for its regulatory regime in good faith, it remains the view of FOEA that a moratorium on the commercial use of manufactured nanomaterials is warranted.

As NICNAS is aware, the gaps in our understanding of nanomaterials' biological behaviour and new toxicity risks is large, and our capacity to measure, assess, compare and mitigate these risks is in its infancy. There has been acknowledgement by leading researchers and the European Food Safety Authority (EFSA) that the extent of uncertainty is such that design of reliable risk assessment systems for nanomaterials is not yet possible (EFSA 2009; Hansen 2009; Oberdörster *et al.* 2007). Furthermore, there are predictions from key international nanotoxicologists that validated nano-specific risk assessment methodologies may take up to 15 years to develop (Maynard *et al.* 2006).

EFSA has stressed that current uncertainties about nanomaterial behaviour compromise our capacity to design a risk assessment process in which we can have confidence, and that is capable of guaranteeing safety:

"Although, case-by-case evaluation of specific ENMs may be currently possible, the Scientific Committee wishes to emphasise that the risk assessment processes are still under development with respect to characterisation and analysis of ENMs in food and feed, optimisation of toxicity testing methods for ENMs and interpretation of the resulting data. Under these circumstances, any individual risk assessment is likely to be subject to a high degree of uncertainty. This situation will remain so until more data on and experience with testing of ENMs become available" (EFSA 2009, p2-39).

For these reasons, FOEA wishes to emphasise, as we have previously, that it is not yet appropriate to allow nanomaterials' commercial use, and that governments should institute a moratorium on the commercial use of manufactured nanomaterials, until the safety science catches up and until it becomes possible to design risk assessment and regulatory regimes in which both technical experts and the wider public can have confidence. Nonetheless, we recognise that irrespective of early signs of the potential for serious harm, and the extent of persisting uncertainty, there is considerable economic and political pressure to increase the pace of commercialisation of manufactured nanomaterials. We therefore make this submission in the hope of helping strengthen the fledgling regulatory systems established to oversee them.

Nano-forms of existing chemicals pose the greatest regulatory challenge

The points made in this submission relate to nano-forms of both new and existing chemicals. The regulation of new nano-chemicals such as fullerenes and some forms

of carbon nanotubes poses considerable challenges. Nonetheless, these nano-chemicals, which have their own CAS numbers, are in the clear minority. The vast majority of the nanomaterials in commercial use are nano-forms of existing chemicals. We therefore fully support the principle of an integrated approach for industrial nanomaterials within the NICNAS framework, recognising that the same approach should be taken to assessing the safety of nano-forms of new chemicals, and nano-forms of existing chemicals.

While we recognise that an integrated regulatory approach to nanomaterials will require new legislation, which will take time, it is imperative that NICNAS ensure that nano-forms of existing chemicals face mandatory notification and assessment as soon as possible. In the short term, this may require NICNAS to issue secondary notifications to all manufacturers/ notifiers whose products may contain a nano-component, requiring them to investigate the properties of their products (see discussion following). However we agree that proceeding with the "Stream 2" proposal canvassed in the Discussion Paper is desirable in the longer term.

The overarching principles of the NICNAS regulatory strategy

A specific commitment to prioritising public interest management of nanomaterials is required

FoEA is concerned that the overarching principles of the NICNAS regulatory strategy ('the principles', Attachment 1) do not make an explicit commitment to prioritise the public interest and protection of the environment. Conversely the principles state that when reviewing regulatory frameworks, "it is prudent to ensure that" "industry innovation is supported through an appropriate level of regulatory oversight". We recommend strongly that the reference to supporting industry innovation is removed from the principles. The NICNAS website (NICNAS undated) states that:

"Our mission is the integrated regulation of industrial chemicals for the protection of human health and the environment through scientific excellence and regulatory efficiency to deliver the safe and sustainable use of chemicals".

Whereas regulatory efficiency is a stated component of the NICNAS mission, fostering industry innovation is not, and should not be a factor in NICNAS' regulatory oversight of nanomaterials.

FoEA is also concerned that the principles do not include any commitment to transparency, and the public and workers' right to know, in relation to nanomaterials regulation and assessment. Because nanomaterials may be toxic in minute amounts and may persist for long periods in the environment, the food chain or human tissue, it is particularly important that accurate information concerning their quantities, properties, location, and regulatory status be freely exchanged and widely accessible to the public. It is therefore essential to enshrine the public's right to know in both the principles and the regulatory framework.

The public's right to know must be recognised explicitly and supported practically; this must include labelling

The need for communities to have to information on toxic chemicals has been recognised internationally in several treaties to which Australia is a signatory (Lloyd-Smith 2002). For example Chapter 19 of Agenda 21 from the United Nations Conference on Environment and Development (UNCED 1992) emphasises the right of the public to information on toxic chemicals, and the need for government and industry to make such information available to them.

Commercial confidentiality must be limited to ensure that the public has access to information on the identity, amount, location and properties of nanomaterials in commercial use, in storage, in transit, in the environment, and other information relevant to protection of human health and the environment. We suggest that as with the Rotterdam Convention which sets minimum standards for inter-governmental information exchange on banned and severely restricted substances, the kinds of information about nanomaterials that should not be considered confidential are:

(1) Use or uses of the chemical [nanomaterial];
(2) Estimation of quantities of the chemical [nanomaterial] produced, imported, exported and used;
(3) Physico-chemical, toxicological and ecotoxicological properties;
(4) Information contained in safety data sheets;
(5) Hazard classification;
(6) Information on precautionary measures;
(7) Information on regulatory actions;
(8) Information submitted by other Parties, international organizations, non-governmental organizations or other relevant sources;
(9) Information on alternatives and their relative risks, and industrial practices and processes, including cleaner technology.

We also emphasise that in order for such information to be readily accessible to the general public, NICNAS should allocated resources to establish readily searchable, web-based databases. This could be based on the United States Environmental Protection Agency's Toxics Release Inventory available at: http://www.epa.gov/tri/.

Furthermore, labelling both industrial chemicals that contain nanomaterials and consumer goods in which nanomaterials are found is essential for public health and safety, environmental and consumer choice reasons. Awareness of the existence of nanomaterials in workplaces is absolutely essential to avoid unsafe nano-exposure and to enable efforts to improve workplace safety. This requires clear product labelling, as well as access to relevant MSDS and safe handling information. Further, consumer product labelling is not only necessary to enable consumer choice, but also nano-aware product handling and disposal. It will also be pivotal to enabling any adverse effects to be traced back to their point of exposure.

We understand that NICNAS has limited regulatory authority for product labelling. Nonetheless, NICNAS will be the regulator with the most access to information about nanomaterials in commercial use, and is ideally placed to support a nano-product labelling initiative. We therefore strongly encourage NICNAS to initiate a joint program with ACCC and SafeWork Australia to ensure that nano-product and industrial chemical labelling proceeds in a timely way.

The precautionary principle should guide NICNAS' oversight and decision making regarding nanomaterials

The principles do not include any commitment to use the precautionary principle. Principle c of Attachment 1 states: "Where best available scientific evidence is insufficient to support the safety of the product/ chemical, measures to protect public health and safety and the environment can be adopted". However this is a weak and equivocal statement, which should be rephrased to state:

> "Where best available scientific evidence is insufficient to support the safety of the product/ chemical, measures to protect public health and safety and the environment will be adopted, in accordance with the precautionary principle."

The precautionary principle has a long history of use in Australian law. It has been included either specifically or by inference as part of ecologically sustainable development in at least 45 Australian environmental statutes at a federal and state level. These are documented in Appendix 1 (From Appendix A, Peel 2005).

The *National Strategy for Ecologically Sustainable Development* (Commonwealth of Australia 1992) adopts the precautionary principle as a "guiding principle" of ecologically sustainable development as does the Inter-Governmental Agreement on the Environment (1992), which is the basis for the distribution of governmental responsibility for environmental management in Australia.

The *National Strategy for Ecologically Sustainable Development* cites the precautionary principle as: "Where there are threats of serious or irreversible environmental damage, lack of full scientific certainty should not be used as a reason for postponing measures to prevent environmental degradation".

The *Environment Protection and Biodiversity Conservation Act* (1999), Australia's central piece of environmental legislation, defines the precautionary principle very similarly: "If there are threats of serious or irreversible environmental damage, lack of full scientific certainty should not be used as a reason for postponing measures to prevent environmental degradation".

FoEA suggests that precautionary principle was developed specifically to guide governance responses when dealing with serious but uncertain risks, as we face with nanotechnology. The common test for whether or not it is appropriate to apply the precautionary principle to a given decision making process is twofold. Firstly, is there evidence of a threat of serious or irreversible harm; and secondly, does scientific uncertainty surround the issue in question? Nanotechnology meets both aspects of this test. There is preliminary evidence of serious health and environment risks associated with manufactured nanomaterials (RCEP 2008; SCENIHR 2009), acknowledgement by leading researchers that the extent of uncertainty is such that even design of reliable risk assessment systems for nanomaterials is impossible (EFSA 2009; Hansen 2009; Oberdörster *et al.* 2007) and predictions that validated nano-specific risk assessment methodologies may take up to 15 years to develop (Maynard *et al.* 2006).

The need to adopt the precautionary principle to manage the serious but uncertain risks associated with nanotechnology has been recognised explicitly by governments from 5 continents. At the 2008 International Forum on Chemical Safety in Dakar 71 governments, 12 international organisations and 39 NGOs recommended "applying

the precautionary principle as one of the general principles of [nanotechnology] risk management" (IFCS, 2008).

Swiss Re, one of the world's largest reinsurance agents, has also called explicitly for application of the precautionary principle in management of nanotechnology risks. In its detailed report into nanotechnology Swiss Re (2004, p 47) warns: "In view of the dangers to society that could arise out of the development of nanotechnology, and given the uncertainty currently prevailing in scientific circles, the precautionary principles should be applied whatever the difficulties".

Friends of the Earth suggests that it is essential to adopt the precautionary principle in the overarching principles of the NICNAS regulatory strategy and in the subsequent formalisation of the NICNAS regulatory approach. In our view, application of the precautionary principle to nanomaterials risk assessment would require manufacturers to provide evidence of safety that is specific to the nanomaterials that are the subject of their application. That is, the burden of proof of safety would rest with proponents. Furthermore, testing and safety data provided for assessment would relate to nanomaterials that have not only the same chemical composition of the nanomaterial for which the applicant is seeking permission to se commercially, but also the specific physico-chemical characteristics (eg size, shape, surface charge, surface structure, coatings, particle size distribution, catalytic properties, solubility etc). If, as is usually the case, relevant or adequate testing has not been performed on the nanomaterial in question (eg if the only safety data provided relates to nanomaterials of the same chemical composition but with different physico-chemical properties), permission for commercial use would be denied.

Standardised nano-specific safety assessment is required, even where assessments are made on a case by case basis

The NICNAS principles state that "risk assessment should be undertaken on a case-by-case basis". FoEA recognises that effective safety and risk assessment requires individual scrutiny of each nanomaterial, given the influence that diverse physico-chemical properties have on toxicity. It is clearly inappropriate to treat as equivalent the risks associated with all nano-forms of a given substance, and as stated above we believe that safety data submitted to NICNAS must pertain to the nanomaterial in question. However we wish to emphasise that a standardised assessment regime is required to underpin and give credibility to case by case assessment. Assessments that are conducted at the discretion of the regulator, with varying standards and breadths of documentation required, tend to lack credibility. In order to ensure a high degree of public confidence in the assessment regime, a standard set of physico-chemical characterisations should be made, as well as a standard set of tests to evaluate the safety or otherwise of the nanomaterial in question. Both of these must be made publicly available.

FoEA suggests that it would be appropriate to involve interested stakeholders and members of the public in determining the appropriate range of physical and chemical properties required for the hazard characterisation of manufactured nanoparticles and the range of safety tests appropriate.

As a first suggestion, we observe that the European Food Safety Authority (EFSA 2009) recommended that nano-specific risk assessment characterise the following:

- Particle size (including distribution of particle size within the sample)
- Surface area and specific surface area of particles
- Shape (including aspect ratios such as fibre-like structures where appropriate)
- Chemical composition (including impurities and processing chemicals)
- Surface properties (e.g. coating, charge, surface adsorption properties)
- Solubility (in fats and water)
- Agglomeration/ aggregation and
- Biodegradability and biopersistence

The European Commission's SCENIHR (2007) has suggested that the following properties are necessary for hazard characterisation:

- Elemental composition;
- Density;
- Crystal structure;
- Solubility;
- Charge;
- Conductivity;
- Melting point;
- Hardness;
- Magnetic and optical properties;
- Morphology;
- Size and size distribution;
- Surface area and surface layer composition;
- Photo-activation; and
- Potential to generate reactive oxygen species.

SCENIHR notes that where relevant, the description of these characteristics needs to take into account known or anticipated variations over time and under varying conditions. This is particularly important given that nanomaterials are likely to vary considerably in form, function and toxicological risk throughout their life cycle. FOEA emphasises that hazard characterisation and risk assessment must take into account the conditions in which nanoparticles are used, for example their interaction with other ingredients in the product in which they occur or the workplace in which they are handled. This is essential given preliminary evidence that many industrial chemicals or cosmetics that NICNAS regulates will contain solvents or substances that act as penetration enhancers. Many secondary sunscreens contain substances that are known to act as chemical penetration enhancers (Pont *et al.* 2004). Furthermore, preliminary research has shown that the co-occurrence of industrial solvents (Xia *et al.* 2010) and surfactants (Monteiro-Riviere *et al.* 2006) greatly increases skin permeability of nanomaterials.

Metrics should be appropriate for nanomaterials – that is, number of particles and particle surface area, rather than weight.

The public benefits of commercial nanomaterial use should be assessed, not assumed

FOEA is concerned that in its Discussion Paper, NICNAS suggests that commercial use of nanomaterials will offer economic and social benefits, although acknowledging that such use may pose new health and environment risks. This 'benefits versus

risks' framing of nanotechnology's challenges is very problematic, as it ignores completely the potential for nanotechnology's use to result in social and economic costs or other more transformative impacts. Furthermore, claims or expectations of social or economic benefit are assumed, rather than being subject to the same sort of careful assessment to which claims or expectations of risk are subject. We are concerned that unscrutinised claims of social or economic benefit may be used in a regulatory impact statement to 'counterbalance' potential risks associated with nanomaterials' commercial use. This would be inappropriate, without also evaluating the social or economic costs that may follow nanomaterials' use, and without assessment of other, less risky options to achieve claimed public benefits.

FOEA suggests that it is not appropriate for nano-products that offer negligible public benefits, for example light-diffracting cosmetics, fullerene-containing anti-ageing creams or odour-eating socks, to pose new health and environment risks. Even if the risks are low, they are unacceptable because there is no public health benefit to be derived from the product's use. Furthermore, the potential for such products to pose broader social costs must be investigated.

The use of nanosilver in clothing is a useful example. Its capacity to reduce odour has resulted in the growing use of silver nanoparticles in socks, high end wool-wear, sporting clothing and work wear. Yet Benn and Westerhoff (2008) have demonstrated that nanosilver treated socks can release up to 1300 µg/L silver following washing, with at least some of that released as nanoparticles of silver. Asharini *et al.* (2008, p7) caution that given their findings of nano-silver's adverse impacts on aquatic organisms: "all applications involving silver nanoparticles should be given special attention and promoted only after detailed studies. The release of untreated nanoparticle waste to the environment should be restricted for the well being of human and aquatic species." Furthermore, beyond its potential acute toxicity, the growing use of antibacterial nanomaterials may have a broader social cost. The president of the Australian Society for Microbiology, Professor Hatch Stokes, and microbiologist Professor Peter Collignon of Canberra Hospital, have publicly agreed with FoEA that widespread use of antibacterial nano-silver could result in dangerous bacterial resistance that would compromise the use of nano-silver in a medical setting where it is of most use (ABC Online 2009, AM 2009)

Professor Peter Collignon agrees nano-silver should be used sparingly to avoid resistance developing. "If you overuse [silver biocides] you do run the risk of getting cross-resistant bacteria developing that are not only resistant to silver, but to other compounds including antibiotics," says Professor Collignon. "The more you use, and the more widespread its use, the bigger that risk." Toxicologist, Dr Paul Wright of Royal Melbourne Institute of Technology also told ABC Online (2009) that he agrees nano-silver shouldn't be used "needlessly". ""We don't need nano-silver in every product," says Wright, who is researching nano-silver with CSIRO, which he says hopes to use nano-silver in biosensors. He says different products shed different amounts of nano-silver, with some brands of socks losing it all after just four washes."

It is FOEA's view that given that odour reduction offer small benefits to the individual wearing the clothing, but poses social costs to the wider public, including threatening the efficacy of life-saving use of antibacterial nanoparticles or antibiotics in a medical setting, the social costs outweigh the social benefits. Further, less-risky and socially costly options exist. Odour in clothing can be reduced regular washing, or employ of non-toxic antibacterials such as tea tree or eucalyptus. We therefore strongly back the calls for restriction of nano-silver's use in frivolous applications, as made by medical experts cited above. The use of nano-silver in clothing should not be

permitted until such time as further research may demonstrate that it does not pose unacceptably high risks to human health and the environment, and will not compromise public health more broadly. We emphasise that the reasons for this are not only the toxicological risks for human health and the environment, but also the social costs of nano-silver's use in products which deliver negligible public health benefit.

A formal review of the NICNAS regulatory framework should be required two years after its commencement

As noted above, the European Food Safety Authority (EFSA) and international nanotoxicologists have warned that given the significant uncertainty surrounding nanomaterials toxicity and biological behaviour, and lack of understanding regarding how best to characterise and analyse them, design of reliable risk assessment processes is not yet possible (EFSA, 2009; Hansen, 2009; Oberdörster *et al.* 2007). It is highly likely that NICNAS will gain considerable knowledge and improved understanding of the logistical and technical challenges of administering a regulatory regime through its first two years' oversight of nanomaterials. It is also very likely that other international regulators will have similar new insights, and that work in the fields of nanotoxicology, metrology, measurement and characterisation will also have progressed considerably. For these reasons, we urge NICNAS to commit to a formal review of its new regulatory framework two years after it commences operation.

Definitional issues

Manufactured particles measuring 0.3nm to 300nm in size should be recognised as nanoparticles, including existing chemicals in this size range

FoEA recognises that any size-based definition of nanoparticles will be to some extent arbitrary, as size is a crude index of novel properties and biological behaviour. Nonetheless, size is one of the primary emerging definitions of nanoparticles and it is important to ensure that the definition for size captures size ranges in which novel nanoscale properties are regularly observed. However, NICNAS' proposed size-based definition of 1-100nm for nanoparticles is too narrow and excludes many particles that show novel nano-specific properties, behaviour and toxicity risks.

Friends of the Earth recommends that nanoparticles be defined as particles that:

(i) Measure <0.3 -300nm in one or more external dimension, or that have an internal structure that exists at this scale, and
(ii) For which size affects technological function or properties, or results in a difference in toxicity compared to the chemical in bulk form.

Nanoparticles that measure 1-100nm are the focus of much scientific research and development, and are used extensively in commercial products, because of the novel properties often observed in this range. However there are some examples of smaller nanoparticles (eg fullerenes and single walled carbon nanotubes), and many examples of particles greater than 100nm in size that also exhibit novel, nano-specific features and behaviour. Our concern is that if a narrow definition of '<100nm

in one or more dimensions' is adopted by NICNAS, companies will intentionally use particles a little larger than 100nm, but which exhibit similar novel properties – and potentially similar nanotoxicity risks – because they will not require registration or nano-specific safety assessment. Consumers, workers, the environment and supply chain handlers would thereby be put at unacceptable risk.

Given the early evidence of their novel, nano-specific behaviour, bioavailability and potential to cause harm, it would be reckless to exclude particles a few hundred nanometres in size from new nanotechnology-specific safety testing requirements and nanoparticle-appropriate exposure metrics. We appreciate that many of the novel properties, biological behaviour and toxicological risk associated with nanoparticles occurs on a sliding scale. However given the step change in bioavailability seen in particles under 300nm being taken up by non-specialist cells, and the existence of novel nano-specific properties and behaviour at this scale, we recommend that this size be used as the upper limit to define nanoparticles.

We understand that it is possible for NICNAS to issue a secondary notification to manufacturers of existing chemicals on a case by case basis, if chemicals are demonstrated to have novel nano-specific properties. However this approach would effectively place the burden for demonstrating novel properties on NICNAS and other interested members of the public. Given resource limitations and difficulties in obtaining relevant information, this approach would therefore likely be very limited in its potential application. As stated by Nohynek *et al.* (2007) many sunscreen companies use zinc oxide particles up to 200nm in size for their transparency, although few disclose the particle size distribution of their products.

In order to ensure that nano-forms of existing chemicals are subject to appropriate nano-specific notification and assessment, we suggest that NICNAS has two key options.

Option 1:

- Where manufacturers are using particles with an average size of 200nm or less, a secondary notification should be issued that requires them to participate in a mandatory nano-specific notification and assessment of their chemicals.
- Additionally, manufacturers using particles of average size 2-300nm will be required to investigate and report the properties of their particles. If manufacturers can demonstrate that their chemicals meet the following two criteria, they will be permitted to retain their existing approvals for chemical use without undergoing nano-specific notification and assessment:

(i) There are no novel properties in their chemical compared to that of the bulk chemical, and

(ii) The nanoparticle component/ contamination of their product is not substantial. We suggest that an acceptable nanoparticle component/ contamination is <5% particles that measure 100nm or less in one or more external dimensions, or <50% particles that measure 200nm or less in one or more external dimensions.

Option 2:

Where manufacturers are using particles with an average size of 300nm or less, a secondary notification should be issued that requires manufacturers/ importers to investigate and report the properties of their chemical. If manufacturers can demonstrate that their chemicals meet the following two criteria, they will be

permitted to retain their existing approvals for chemical use without undergoing nano-specific notification and assessment:

(i) There are no novel properties in their chemical compared to that of the bulk chemical, and

(ii) The nanoparticle component/ contamination of their product is not substantial. We suggest that an acceptable nanoparticle component/ contamination is <5% particles that measure 100nm or less in one or more external dimensions, or <50% particles that measure 200nm or less in one or more external dimensions.

This screening process would be efficient, yet would require manufacturers to investigate their chemicals, and to ensure that there are not unexpected novel properties, or an unexpected nanoparticle component or contamination of their products. Such a requirement is warranted given recent evidence that many particles a few hundred nanometres in size show unexpected novel nano-specific behaviour and pose nanotoxicity risks.

Particles >100nm are regularly used for their novel, nano-specific properties

The proposed NICNAS definition of nanoparticles as measuring <100nm in one or more dimensions will exclude from notification and assessment many particles that are used routinely in commerce for their novel, nano-specific properties. Some examples of particles that measure greater than 100nm and that exhibit novel nano-specific properties include:

Multi-walled carbon nanotubes: many have a diameter greater than 100nm

Carbon nanotubes possess novel mechanical, chemical, electrical, thermal, and optical properties compared to carbon in bulk form (Sinnott and Andrews 2001). Multi-walled carbon nanotubes (MWCNT) generally comprise 2 to 50 concentrically stacked cylinders of single-walled carbon nanotubes (SWCNT) that measure up to a few nanometres in diameter (Poland *et al.* 2008). Importantly, MWCNT generally range from 10-200nm in diameter (Donaldson *et al.* 2006). In their study into the potential of MWCNT to induce mesothelioma-like effects in mice, Poland *et al.* (2008) measured one of the two long MWCNT samples tested to have a diameter of 165.02 ± 4.68nm (Poland *et al.* 2008). More than 40% of the commercial MWCNT tested by Takagi *et al.* (2008) had a diameter greater than 100nm.

Nano zinc oxide: many commercially used nanoparticles are greater than 100nm

Nanoparticle zinc oxide is commonly used as a UV absorber in sunscreens, cosmetics, paints and fabric coatings due to the transparency of zinc at the nanoscale. Nohynek *et al.* (2007) note that for this purpose, zinc oxide particles are typically 30-200nm in size. BASF (2007a), manufacturer of ingredient Z-cote (transparent nano-zinc), states that its product has an average particle size of 140nm; only about 20% of particles measure less than 100nm. BASF (2007b) states that below about 200nm, zinc oxide particles become transparent.

Medical nanoparticles: normal size range is up to 250nm

The useful size range of nano-medicines normally falls within the range of 5–250 nm as these tend to have a similar range of properties based on physiological and anatomical consequences, including very high bioavailability (Garnett and Kallinteri 2006). Nanomaterials being developed for clinical applications include liposomes measuring 100-200nm, nanoshells measuring 60-400nm (Portney and Ozkan 2006) and drug delivery systems measuring 100-200nm (Higaki *et al.* 2005), among others.

Metal nanoparticles are of considerable interest for Surface Enhanced Raman Spectroscopy (SERS), which has potential applications in medical imaging but also analytical chemistry and biological imaging. Fang *et al.* (2008) showed recently that when using gold nanoparticles, the nanoparticle film with the size range of 120–135 nm showed the highest SERS activity.

Particles >100nm can pose novel, nano-specific toxicity risks

Particles up to a few hundred nm in size share many of the novel biological behaviours of nanoparticles <100nm in size, including very high reactivity, bioavailability, increased influence of particle surface effects, strong particle surface adhesion, strong ability to bind proteins and very high bioavailability (Cedervall *et al.* 2007; Garnett and Kallinteri 2006; Linse *et al.* 2007). As with even smaller particles, particles up to 300nm in size can be taken up into individual cells by pinocytosis (Garnett and Kallinteri 2006; specialist cells such as macrophages can take up particles 0.25–10 µm in size). Latex spheres up to 200nm in size can be transported along neurons from the nose to the brain, accessing the central nervous system (Katz *et al.* 1984).

There is no neat cut off point at which nanotoxicity risks are no longer present. As Donaldson *et al.* (2001) observe "There is no reason at the moment to think that there is much difference between a 90 nm and a 110 nm particle in ability to have an adverse effect and there is little evidence for the [100nm] cut off point for the ultrafine effect." At aural hearings last year for the United Kingdom's House of Lords Inquiry into nanotechnology and food, Professor Ken Donaldson told the Inquiry that "there is no toxicological basis whatsoever" for the emerging definition of a nanoparticle as a particle with at least one dimension <100nm:

"The idea that a 102 nm particle is safe and a 99 nm particle is not is just plain daft, it does not work that way. It is a sliding scale: … as particles get smaller their surface area per unit mass increases; and it is surface area that interacts with biological systems..." (UK House of Lords 2009a). Professor Donaldson urged the Inquiry "not to be too hung up" on the 100nm definition, but to be also concerned about particles 200nm in size. He said that he didn't know where the cut-off point was to define 'bulk' or 'natural' size, "but certainly we should not be too struck on the idea that 100 nanometres means harmfulness beneath it and harmlessness above it" (UK House of Lords Inquiry 2009b).

At the same Inquiry, Dr Jonathon Powell confirmed that he considered particles with an average diameter of 200nm to be larger nanoparticles that should be treated as nanoparticles (UK House of Lords 2009c).

Studies finding that carbon nanotubes can cause the same disease as asbestos fibres received world wide attention (Poland *et al.* 2008; Takagi *et al.* 2008). Yet many of the nanotubes in the studies measured >100nm and so would not be considered to be 'nanomaterials' using a <100nm size-based definition. Poland *et al.* (2008) found that two samples of long, tangled multi-walled carbon nanotubes caused asbestos-like pathogenicity when introduced into the stomachs of mice. As stated above, one of their two samples had a mean diameter of 165nm and a length of greater than 10µm. Similarly, Takagi *et al.* (2008) found that in a long term study, more mice died from mesothelioma following exposure to multi-walled carbon nanotubes than died following exposure to crocidolite (blue) asbestos. In this study >40% of the commercial nanotubes sampled had a diameter >110nm.

Several studies have reported nanomaterial-like biological behaviour in particles 200nm in size - suggesting strongly that even 200nm is not an appropriate upper limit for defining nanoparticles. In an *in vitro* study Ashwood *et al.* (2007) found that 200nm particles of titanium dioxide adsorb bacterial fragments to their surface and 'smuggle' these into human intestinal tissue where they mimic invasive pathogens and can provoke inflammation. Linse *et al.* (2007) found that in an *in vitro* study, along with smaller nanoparticles, the large surface area and surface charge of 200nm nanoparticles catalysed protein fibrillation (mis-folding). Protein fibrillation is involved in many human diseases, including Alzheimer's, Creutzfeld-Jacob disease, and Type 2 diabetes. Cedervall *et al.* (2007) also found strong interactions between proteins and 200nm particles.

'Substances with nanomaterial properties' must be referred for nano-specific notification and assessment

Particle size is a useful but incomplete index of novel properties. The use of any particular size-based definition of nanoparticles will not encompass all particles that show novel nano-specific behaviour. This makes it essential to have a mechanism to refer for nano-specific assessment and registration particles that show novel, nano-specific properties or behaviour, but that fall outside the size range cited in the definition. A 'novel properties' trigger could therefore supplement the size-based trigger for nano-specific notification and assessment.

FoEA therefore recommends formal recognition of 'substances with nanomaterial properties'. There will be substances that may fall outside the size range NICNAS or FOE proposes to use to define 'nanomaterials', but which nonetheless exhibit nano-specific behaviour – eg novel optical, electrical, chemical or tensile properties, very high reactivity, bioactivity and bioavailability, increased influence of particle surface effects, strong particle surface adhesion and/ or strong ability to bind proteins. We recommend that if a material is recognised as a 'substance with nanomaterial properties' it must be assessed using safety testing procedures and metrics developed for nanomaterials.

Recognising 'substances with nanomaterial properties' that fall outside the size-based definition of nanomaterials will be especially important if the more narrow definition of nanomaterials measuring <100nm in at least one dimension, or even <200nm in at least one dimension, is adopted. As noted, some of the nanomaterials about which the most serious safety concerns exist - for example multi-walled carbon nanotubes that produce mesothelioma in test mice – measure greater than 100nm in

their smallest dimension. It is essential that we have a mechanism to refer such substances for appropriate, nano-specific safety assessment.

Soluble and partially soluble nanoparticles must be defined and assessed as nanoparticles

FoEA strongly advises that it is inappropriate to introduce a definition that excludes soluble nanoparticles from assessment as 'nanoparticles'. Water soluble and partially soluble metal and metal oxide nanoparticles can pose significant toxicity that is a product of both ion and particle effects, and which is greater than that observed from the release of ions alone (Asharini *et al.* 2008; Bai *et al.* 2009; Brunner *et al.* 2006; Griffitt *et al.* 2009; Limbach *et al.* 2007). Water soluble fullerenes can also pose serious toxicity (Sayes *et al.* 2004).

Furthermore, solubility is an inappropriate criterion for definitional purposes as the solubility of nanoparticles in water and their rate of dissolution is complex and remains poorly understood (SCENIHR 2009). For example the reported solubility of zinc oxide has varied given different experimental conditions such as particle size, suspending medium, temperature, pH and ultrasonic parameters (Bai *et al.* 2009). Dissolution of partially soluble nanomaterials is also complicated by concomitant agglomeration and aggregation (Griffitt *et al.* 2009). Use of the standard OECD test guidelines for measuring materials solubility is unlikely to provide the required information for nanoparticles (SCENIHR 2009). Particle dissolution in cells is also influenced by the route of cellular uptake, the presence of proteins and other organic substances, particle concentration and material characteristics (Xia *et al.* 2008). This means that establishing the water solubility of a given particle does not necessarily provide an accurate measure of the particle's solubility in the environment or *in vivo*, and hence its likely exposure potential or biopersistence.

In its opinion on the risk assessment of nanotechnologies the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR 2009, p52) stated that:

"For (partially) soluble nanomaterials the toxicity may be governed at least in part by the soluble species/fraction released from the nanomaterial. For low solubility or a slow release, the particulate nature of the substance may be relevant with regard to potential tissue distribution and local release of toxic species which should then be considered in the risk assessment of such nanomaterials."

The indicative list of nanomaterials provided by NICNAS in Attachment 2 suggests that excluding partially or sparingly soluble nanomaterials from assessment is not NICNAS' intention. However defining nanoparticles as wholly insoluble (<1mg/L) would have this effect. The only rationale for using a definition that excludes all but the most absolutely insoluble of nanoparticles would be that if nanoparticles are even partially water soluble, their characteristics over time will eventually resemble those of the bulk chemical, so that traditional risk assessment procedures are appropriate. This would go well beyond the SCENIHR's qualified advice that the toxicity of "(partially) soluble" nanomaterials may be governed "at least in part" by understanding of the toxicity of the bulk material's ions or soluble fraction. We understand that the solubility threshold proposed by NICNAS of 1mg/L is based on advice provided by the European Chemicals Bureau (2003, p258) that particles under 1µm in size and with this solubility or less pose the greatest accumulation

potential. However this advice was provided before many of the very recent nanotoxicology work was completed and does not appear to take into account any of the novel behaviours, biokinetic properties and bioavailability of nanomaterials. We suggest that not only could nanomaterials with a higher solubility accumulate, even where significant accumulation does not present the risk of long-term pathologies, acute nanotoxicity will still be an issue that requires careful assessment by NICNAS.

A 1mg/L solubility threshold dismisses the possibility that partially soluble nanoparticles will exert particle-mediated toxicity. For example, the United States Environmental Protection Agency (US EPA 1995) states that the reported water solubility of zinc oxide ranges from 1.6 to 5 mg/L, above the threshold of insolubility proposed by NICNAS. Yet the literature provides evidence that in nanoparticle form zinc oxide, silver, copper, cobalt oxide, manganese oxide and other soluble and partially soluble materials exert both ion and particle-mediated toxicity (Asharini *et al.* 2008; Bai *et al.* 2008; Brunner *et al.* 2006; Griffitt *et al.* 2009; Limbach *et al.* 2007; Sayes *et al.* 2004; Xia *et al.* 2008) and accumulate in the organs, cells and cell nuclei of exposed animals (Asharini *et al.* 2008; Griffitt *et al.* 2009; Limbach *et al.* 2007). Although the solubility of these nanomaterials is not stated in the literature cited, given the substantive ion-formation observed in many of these studies, it seems probable that solubility is >1mg/L.

In their survey of 7 industrially relevant nanoparticles, Brunner *et al.* (2006) suggested that mechanisms of toxicity for partially soluble nanoparticles include: the release of ions, particle surface catalysed reactions and formation of reactive oxygen species (ROS), and/ or stress or stimuli caused by the surface, size and/or shape of the particles. They found that iron oxide nanoparticles, although partially soluble, exerted a surprisingly strong cytotoxic effect that was greater than the dissolved iron ions alone. Asharini *et al.* (2008) showed that water soluble silver nanoparticles were far more toxic to developing zebra fish embryos than dissolved silver ions alone, resulting in a high and dose-dependent mortality rate, delayed hatching, DNA damage and chromosomal aberration. Bai *et al.* (2009) found that the toxicity of partially soluble zinc oxide to developing zebra fish embryos was greater than the toxicity to embryos of dissolved zinc ions alone. Griffitt *et al.* (2009) found that exposure of zebrafish to nanoparticles of copper produced significantly more thickening of the gill filaments than did exposure to soluble copper. Xia *et al.* (2008) also observed zinc oxide nanoparticles exerting both ion and particle-mediated toxic effects. They found that solubility increased toxicity: dissolved zinc ions from zinc sulphate were more toxic than the same quantity of zinc in less soluble zinc oxide. Nevertheless, where incomplete dissolution occurred at higher concentrations of zinc oxide nanoparticles, the authors attributed higher cell death to the presence and uptake of solid zinc oxide nanoparticles. In an *in vitro* study, Sayes *et al.* (2004) demonstrated that some forms of water-soluble fullerenes were cytotoxic to human cells at concentrations as low as 20 parts per billion.

Partially soluble nanomaterials may have very different bioavailability, biokinetics and biopersistence compared to ions and soluble forms of the same chemical composition. Griffitt *et al.* (2009) found that exposure of zebrafish to silver nanoparticles resulted in significantly and dramatically higher levels of silver associated with the gills, and significantly increased whole body silver content, compared to exposure to silver ions alone. Asharini *et al.* (2008) found that unlike dissolved silver ions, silver nanoparticles accumulated in the nucleus of cells and the brains of exposed developing zebrafish embryos. Similarly, Limbach *et al.* (2007) found that partially soluble nanomaterials cobalt oxide and manganese oxide were taken up into cells preferentially to their respective ionic forms. Once in the organs, cells or cell nuclei of exposed animals, these nanoparticles could then dissolve and

exert ion-mediated toxicity, or persist for some time exerting particle-mediated toxicity.

Even wholly soluble nanomaterials made of non-metal substances (eg micelles, nano-liposomes and nano-encapsulated active ingredients) possess novel properties and biological behaviours compared to larger forms of the same substances, and therefore must be included within the definition of 'nanoparticles' and subject to nanotechnology-specific risk assessment and exposure metrics. Researchers and companies are interested in nano-sizing or nano-encapsulating food, cosmetic, industrial chemical and agricultural product ingredients including vitamins, enzymes, preservatives or pesticides precisely because this results in greater bioavailability, improved solubility and increased potency of these substances compared to larger or micro-encapsulated form (Mozafari et al. 2006). Novel nano-formulated soluble materials are already being exploited commercially. For example AquaNova markets its nanoscale micelles for use in foods and cosmetics *because* they deliver "significantly higher bioavailability" of enclosed active ingredients once ingested or applied to the skin (AquaNova undated). Similarly, companies such as Aquanova and Zymes are now selling 30-40nm nano-capsules of Omega 3 because the potency is significantly increased at this scale (Halliday 2007).

The greater bioavailability of nano-encapsulated or nano-formulated soluble materials means that such materials present a different exposure profile to the same substances in bulk form. If nano-formulated soluble materials provide an excessive dose of some active ingredients these may have a toxic effect or interfere with the absorption of other nutrients. Dr Qasim Chaudhry who leads the nanotechnology research team at the United Kingdom's Central Science Laboratory warns that nanoparticle and nano-encapsulated food ingredients "may have unanticipated effects, far greater absorption than intended or altered uptake of other nutrients, but little, if anything, is known currently" (Parry 2006). Given the poor understanding we have of how the far greater bioavailability, solubility and potency of nano-formulated soluble substances will influence their biological behaviour and potential toxicity, it is essential to subject these nanomaterials to new nanotechnology-specific safety assessments and exposure metrics.

For the reasons cited above, it is highly inappropriate to include any reference to solubility in the definition of nanoparticles. However should NICNAS insist on defining nanoparticles as 'insoluble', we urge it to raise the extremely low solubility threshold stated in Attachment 6 of 1mg/L to ensure that partially or sparingly soluble materials are assessed as nanoparticles. Including partially soluble nanoparticles in nano-specific safety assessments is absolutely essential given the evidence cited above that partially soluble nanoparticles can exert significant toxicity through both ion and nanoparticle-mediated mechanisms, and can accumulate in the organs, cells and cell nuclei of test animals.

Biopersistence should not be used to define nanoparticles

Biological persistence should be investigated as part of a nano-specific safety assessment – it should not be a criterion used to define nanoparticles and so to determine whether or not nano-specific assessment is required. Even particles that do not show significant biopersistence may pose acute nano-specific toxicity (eg see the partially soluble nanoparticles studied by Bai *et al.* 2009; Brunner *et al.* 2006 and Xia *et al.* 2008). Furthermore, although biopersistence will be a key factor influencing

the potential of nanoparticles to result in long term pathologies, including carcinogenic, mutagenic, or teratogenic effects (Brunner *et al.* 2006), very little is currently known about the biopersistence of nanomaterials already in commercial use. Nanoparticle toxicology remains at an early stage and the majority of researchers have focussed on the potential for acute toxicity rather than long term persistence. It would be most unfortunate if a nanoparticle was considered to not have biopersistent properties, and therefore not warrant assessment as a nanoparticle, because of inadequate prior study into its biological behaviour.

The biological behaviour of nanoparticles, including biopersistence, may be dependent on a complex range of factors including size, surface area, surface charge and coating, surface modification, interaction with proteins, the state of aggregation or agglomeration (Chen *et al.* 2008) and the route of exposure (Hussain and Schlager 2009). Very few of these variables have been properly studied for any given nanoparticle. SCENIHR (2009) observed that biopersistence of nanomaterials such as carbon nanotubes, nanowires and nanorods will be key to their potential to cause long term harm such as mesothelioma. However, even in relation to these high profile nanomaterials that have been identified as of key concern, very little research has been conducted into biopersistence. Similarly, the biokinetics of quantum dots, which are designed to be injected intravenously for medical imaging, remain little studied (Chen *et al.* 2008).

Finally, biopersistence is not always clear cut; Chen *et al.* (2008) found that over 90% of the quantum dots they injected into mice were excreted within 5 days. However, 8.6% of the quantum dots bound with proteins and persisted in the liver tissue at the close of the experiment. It was not clear whether, or in what time frame, these quantum dots would be cleared. The authors noted that it was also unclear how long the surface coatings providing protection from the cadmium core of the quantum dots would persist.

Aggregates and agglomerates whose primary particles are nanoscale, and particles which possess nano-structures, must be defined and assessed as nanoparticles

FoEA emphasises that agglomerates and aggregates whose primary particles are nanoscale, and particles which possess nano-structures, must be included within the definition of 'nanoparticles' and subject to nanotechnology-specific risk assessment and exposure metrics.

The EU's SCENIHR (2009, p52) notes that:

"…when a nanomaterial is in particulate form, the particles may be present either as single particles or as agglomerates or aggregates. Depending on the nanomaterial the majority of the particles may be agglomerates or aggregates. This may lead to the misinterpretation that agglomerates or aggregates of nanoparticles that have external dimensions well beyond 100nm are not considered nanomaterials. Yet they retain specific physicochemical properties which are characteristic of nanomaterials, most likely due to their large specific surface area (SSA). Therefore, when describing a nanomaterial it is important to describe not only the mean particle size but also the size of the primary particles. In addition, information on the presence of agglomerates or aggregates should be presented".

We also note that the German Chemicals Industry Association (Verband Der Chemischen Industrie) has just released a statement (VCI 2010; Appendix 2) calling for agglomerates and aggregates to be specifically defined and regulated as nanomaterials:

"VCI believes that for a good product stewardship a definition of nanomaterials strictly limited to so called "nano-objects", being particles with one, two or three external dimensions between approximately 1 nm and 100 nm, is not satisfactory. Besides "nano-objects", also larger discrete particles like aggregates and agglomerates of primary particles, which could disintegrate into "nano-objects" or could have a high surface area, should, for good product stewardship, be included in a nanomaterial definition."

Given that Germany is one of the world's foremost investors and developers of nanotechnology, we believe that it is very significant that the VCI has made this call. See also discussion below on the minimum nanoparticle component in a sample that should trigger its regulation as a nanomaterial.

If nanoparticles fuse together, they form aggregates which may be hard to separate. These nano-structured aggregates may be larger than 100nm – or even larger than 300nm. However in many instances aggregates will have close to the same surface area as the nanoparticles they are made from and will have 'nooks and crannies' on their surface structure that are nano-sized (Maynard 2007). Where toxicity is driven by surface characteristics, the toxic properties of aggregated nanoparticles may be very similar to that of the primary nanoparticles that compose them. In fact some early studies exposing animals to large nanoparticle aggregates showed effects that appeared to be associated with these primary particles, although the primary particles were more potent in many respects (see reviews in Maynard and Kuempel 2005; Oberdörster *et al.* 2007). Bai *et al.* (2009) found that although in solution the nanoparticle zinc oxide they studied readily formed clusters of small and large aggregates, the (aggregated) nanoparticle zinc oxide exerted a greater toxic effect on developing zebra fish embryos than the corresponding concentration of zinc ions. Griffitt *et al.* (2009) also found that in solution nano-silver and nano-copper readily formed polydisperse suspensions that contained a range of sizes, including a substantial number of aggregates and agglomerates >100nm in size. Nonetheless, nano-copper was significantly more toxic to the exposed zebrafish than dissolved copper ions alone, and nano-silver resulted in a dramatically higher silver gill content and silver body burden than dissolved silver ions alone.

In other instances, nano-structured aggregates have resulted in greater damage than that associated with the primary nanoparticles. In an inhalation study using mice Shvedova *et al.* (2005) found that aggregates of single walled carbon nanotubes were the focal point of granulomatous inflammation. In their study of the biokinetics of quantum dots, Chen *et al.* (2008) found that aggregates of silica-coated cadmium quantum dots that had bound with proteins had the greatest biopersistence and therefore presented the most serious potential future risk should their coatings degrade.

Nanoparticles that form clusters but do not adhere so strongly together are called agglomerates. Agglomerates have similar structures and surface properties to aggregates and so may also share the toxicity risks associated with the primary nanoparticles that compose them. Importantly, in principle agglomerates are more likely to change shape or to come apart than aggregates (Maynard 2007, see below). However if particles do not de-agglomerate, as with aggregates their size can reduce their bioavailability relative to that of their primary nanoparticles (Limbach *et al.*

2005). Large agglomerates also have a reduced surface area compared to that of their primary nanoparticles when dispersed. This can reduce the biological activity and toxicity of agglomerates compared to their primary nanoparticles (Sager *et al.* 2007), although agglomerates may remain more toxic than (larger) primary particles. Nonetheless, agglomeration does not necessarily reduce particle toxicity. For example Muller *et al.* (2005) found that 2 months after intratracheal installation of multi-walled carbon nanotubes in rats, pulmonary lesions were caused by the accumulation of large carbon nanotube agglomerates in the airways.

It is still largely unknown to what extent aggregates and agglomerates will break down into smaller particles in our bodies, eg after inhalation. Researchers routinely use surfactants to 'debundle' single and multi-walled carbon nanotube samples for physicochemical investigation (Blackburn *et al.* 2006, Lisunova *et al.* 2006). Biological fluids, eg the lung's epithelial lining fluid which contains both surfactants and proteins, may similarly promote de-agglomeration (Maynard 2007, Oberdörster *et al.* 2007) or even break up of aggregates (Donaldson *et al.* 2006) into smaller clumps or even into the primary nanoparticles or fibres. For example Maynard (2002) found that larger agglomerates of titanium dioxide broke into smaller agglomerates with a diameter of around 100nm when exposed to a synthetic lung surfactant. Vigorous agitation also leads to disaggregation of nanotube clumps and the production of particles smaller than 100nm (Maynard *et al.* 2004).

The poor understanding we have of disaggregation and de-agglomeration processes and the early evidence that aggregates and agglomerates may share many of the surface characteristics and toxic properties with the primary nanoparticles that compose them demand that we treat these particles as nanoparticles, as recommended by the SCENIHR (2009) and the German Chemicals Industry Association (VCI 2010).

5% of particles <100nm, or <50% of particles 200nm should trigger nano-specific regulation

The manufacture and fabrication of particles is imprecise. Eg Poland *et al.* (2008) found a substantial difference between the actual dimensions of the nanotubes and the dimensions claimed by the manufacturer. Many manufacturer use particles with a very wide particle size distribution, that still deliver novel nano-properties (eg BASF's Z-cote nanoparticle zinc oxide product that provides transparent UV protection, while containing only 20% particles <100nm; BASF 2007a). Further, it is likely that many other manufacturers have such a wide particle size distribution that their products do not show obvious novel nano-specific novel properties, but which nonetheless introduce novel health and environmental risks (eg a sunscreen that contained 20% particles <100nm, but 20% particles >300nm may not be transparent, but may nonetheless introduce nano-specific health risks). For these reasons it is important to clarify what is the smallest proportion of a sample being present in nanoparticle form that will trigger mandatory notification and assessment.

The only recommendation or precedent in this respect internationally that FOEA is aware of is the statement just released by the German federation of the Chemical Industry (VCI 2010).

VCI recommends that for the purposes of regulation:

"Nanomaterials are defined as intentionally manufactured, solid, particulate substances, either in powder form or as dispersions or as aerosols, consisting of nano-objects and their aggregates and agglomerates,
(i) which contain, when measured by standardised and recognised methods, at least 10 wt.-% of nano-objects,
(ii) or which have, when measured by appropriate methods, a volume specific surface area larger than 6 x 1/100 nm.

Nano-objects are discrete particles with one, two or three external dimensions between approximately 1 nm and 100 nm".

For the reasons stated above, FOEA suggest very strongly that any reference to nanoparticles that excludes soluble nanoparticles is very problematic, as is measuring nanoparticles by weight. Furthermore, given the serious difficulties inherent in accurately characterising and measuring nanoparticle size, as acknowledged by VCI (2010), and the uncertainty over what level of exposure to some nanomaterials may pose health and environment risks, we suggest that a 10% component of nanoparticles is too high to set as a base 'threshold' to trigger nano-specific regulation. We also emphasise that focussing exclusively on particles <100nm in size is inappropriate for the reasons cited above.

We therefore recommend that NICNAS treat as 'nano' samples where:
(i) >5% of the number of primary particles or their agglomerates or aggregates measure <100nm in one or more dimensions; and/ or
(ii) >50% of the number of primary particles or their agglomerates and aggregates measure <200nm.

We recognise that particle surface area is a key factor affecting toxicity for some nanomaterials. However we do not have a firm view on whether it is appropriate and of practical value to include particle surface area in a definition of nanoparticles.

The size threshold at which NICNAS defines nanoparticles is critical. As we have stated above, many manufacturers of materials that NICNAS regulates use particles that measure >100nm, but below a few hundred nanometres, because of their novel properties at this size. If NICNAS fails to include a provision for particles >100nm triggering nano-specific notification and assessment, many manufacturers will choose to use particles >100nm in size that still exhibit novel properties, but that will be exempt from appropriate notification and assessment. In this instance we suggest that case by case reliance on secondary notifications for manufacturers whose products are identified by NICNAS or members of the public as demonstrating novel nano-properties would be cumbersome, inefficient and ineffective.

All nanomaterials should require assessment prior to commercial use; conditions should be attached to R&D use

We agree with NICNAS' proposal to remove the weight thresholds and limits from its different permit and certificate categories and to require all nanomaterials to face notification and assessment prior to commercial use. There is broad agreement that mass is an inappropriate metric for nanomaterials and that particle surface area or particle number are likely to be more appropriate (SCENIHR 2007). There is also

widespread recognition that many nanoparticles pose far greater toxicity than larger particles of an equal mass (eg Maynard 2006).

We strongly support the exclusion of nanomaterials from the low volume exemptions (Attachment 6). The example of fullerene cosmetics is useful to illustrate a nanomaterial of high concern should not be used –albeit in small quantities – in cosmetics or other products, without appropriate notification and assessment. We wish to emphasise that this should not relate only to nanomaterials that are new chemicals, but also nano-forms of existing chemicals. We also support the exclusion of nanomaterials from SAPLC, SANHC and SANHP exemptions.

FOEA support ongoing nanotoxicology and eco-nanotoxicology research and we understand that this will involve hazardous nanomaterials. Nonetheless we are concerned that considerable quantities of nanomaterials are produced, handled and disposed of from public and private research and development facilities. We therefore suggest that it is appropriate that rather than exempting research and development activities entirely, NICNAS should attach conditions to the handling of nanomaterials for R&D purposes, to safeguard the health of researchers, support staff and others in the buildings in which R&D is performed, and environmental systems in to which waste products are released.

Voluntary initiatives on nanotechnology have failed; voluntary co-regulatory options should not be introduced

NGOs including FOEA have been very critical of past voluntary initiatives, and we would not be supportive of NICNAS adopting any voluntary measures as part of the introduction of its new nanotechnology regulatory regime. We are also concerned at the proposal for NICNAS to initiate a voluntary reporting program (Stream 1A) as a precursor to a mandatory reporting program (Stream 1B). Contrary to this building public confidence in NICNAS' oversight of nanomaterials, we suggest that it may simply delay the commencement of a mandatory program, while delivering little new information. It is not clear what information NICNAS hopes to receive as a result of this call, which was not provided in response to either of NICNAS' previous two calls for voluntary provision of nanomaterial use information.

Voluntary initiatives have been launched in the United Kingdom, the United States, Australia and elsewhere to coax industry to make available information regarding its production, handling and use of manufactured nanomaterials. Governments and regulators have largely launched these voluntary reporting programs in the hope of gaining information on which future (potentially mandatory) schemes may be developed. Unfortunately, although not surprisingly, these initiatives have met with clear failure and a marked unwillingness – or incapacity – on the part of industry to provide clear information. Governments in Europe and the United States have acknowledged that even years after beginning voluntary reporting schemes, they have little information regarding the extent to which manufactured nanomaterials are present in commercially traded goods (Breggin *et al.* 2009).

The United Kingdom's two year voluntary reporting scheme resulted in only twelve submissions (Breggin *et al.* 2009), despite the UK Department of Trade and Industry estimating that there are 372 organizations involved in micro- and nano-manufacturing in the UK (Berger 2007). Only 29 companies and trade associations participated in the US EPA's 'Basic Program" as part of the Nanoscale Materials

Stewardship Program (NMSP); another 7 companies committed to submit information at a future date. In its interim report on the NMSP, the US EPA (2009, p27) estimated that this leaves "approximately 90% of the different nanoscale materials that are likely to be commercially available were not reported". Further undermining the usefulness of the scheme, a number of the submissions EPA did receive did not contain exposure or hazard-related data. The EPA also noted that the low rate of engagement – seven companies - in its 'In-Depth Program' "suggests that most companies are not inclined to voluntarily test their nanoscale materials" (US EPA 2009, p27). This phenomenon is not restricted to the United States. A survey of German and Swiss companies found that of those companies who chose to respond, 65 per cent did not perform any risk assessment of their nanomaterials (Helland *et al*. 2008).

We recognise that the most productive action to take at this stage is to develop a mandatory notification and assessment program, with a clear commitment for review two years subsequent to the program's commencement. We would not support any voluntary component of a new NICNAS regulatory framework on nanomaterials, including any form of self-assessment or self-regulation by industry.

A final comment on the use of permit and/ or certificate systems for nanomaterials notification and assessment

Neither NICNAS' permit nor certificate system is appropriate for nanomaterials. For the reasons outlined in the NICNAS discussion paper, permits offer advantages because of the ability for NICNAS to determine conditions, and retain the ability to revoke permits if new information emerges. Nonetheless, permits offer unacceptably low public accountability, and it is not clear that adequate risk information will be provided to NICNAS. We therefore recommend a new permit category for nanomaterials. Demonstration of 'no unreasonable risk' or 'low hazard', as required to approve a permit, must require full, standardised nano-specific health and environmental assessment, where full physico-chemical characterisation is carried out and safety data are specific to the nanomaterial in question (ie not just another nano-form of that chemical composition). Risk assessment reports should be published in full. Further, the issuing of permits, and the related conditions, should be listed on a publicly available database, based on the US EPA's Toxics Release Inventory. Labelling should also be required to alert potentially exposed workers and consumers.

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