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COMMISSION STAFF WORKING PAPER

Types and uses of nanomaterials, including safety aspects

Accompanying the

**Communication from the Commission to the European Parliament, the Council and the
European Economic and Social Committee**

on the Second Regulatory Review on Nanomaterials

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1. INTRODUCTION

The European Parliament in its resolution of 24 April 2009 on Regulatory Aspects of Nanomaterials¹ called on the Commission to compile an inventory of nanomaterial types and uses. In particular, it stated:

“H. whereas there is no clear information about the actual use of nanomaterials in consumer products, for instance:

- while inventories by renowned institutions list more than 800 manufacturer-identified nanotechnology-based consumer products currently on the market, trade associations of the same manufacturers question these figures, on the basis that they are overestimations, without providing any concrete figures themselves,

- while companies happily use “nano-claims”, as the term “nano” seems to have a positive marketing effect, they are strictly opposed to objective labelling requirements,

J. whereas presentations about the potential benefits of nanotechnologies predict an almost infinite diversity of future applications of nanomaterials, but fail to provide reliable information about current uses,

16. Calls on the Commission to compile before June 2011 an inventory of the different types and uses of nanomaterials on the European market, while respecting justified commercial secrets such as recipes, and to make this inventory publicly available; furthermore calls on the Commission to report on the safety of these nanomaterials at the same time”

In its response² of 14 July 2009 the Commission stated in relation to paragraph 16 of the above resolution that “*the Commission intends to present information on types and uses of nanomaterials, including safety aspects, in 2011.*” This formulation was chosen because at the time of the resolution the implications of an “inventory” were unclear and required further

¹ <http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P6-TA-2009-0328&language=EN>

² Follow-up to the European Parliament resolution on regulatory aspects of nanomaterials, adopted by the Commission on 14 July 2009.

analysis, including an analysis of registration dossiers under the first registration deadline of the REACH Regulation³ and of notification dossiers under the CLP Regulation⁴.

In its conclusions on “improving environmental policy instruments” of 20 December 2010⁵, the Council invited the Commission to “*evaluate the need for the development of specific measures for nanomaterials relating to risk assessment and management, information and monitoring, including the further development of a harmonized database for nanomaterials, while considering potential impacts*”.

This Staff Working Paper intends to present available information on types and uses of nanomaterials, including safety aspects and to discuss options for a harmonised database for nanomaterials, considering potential impacts.

In principle, the Staff Working Paper covers nanomaterials within the scope of Commission Recommendation 2011/696/EU on the definition of nanomaterial.⁶ Nevertheless, as the request by the European Parliament is related to nanomaterials on the market, this document focuses on manufactured nanomaterials, and does not cover naturally occurring nanomaterials (e.g. dust, volcanic ash etc.) and incidental nanomaterials (e.g. particulate matter from combustion installations).

The current EU definition of nanomaterial focuses on nanomaterials with a majority of particles in the nanoscale (1 nm to 100 nm). It is noted that particular varieties of many of the particulate materials discussed in this Staff Working Paper may or may not fall under the definition in Recommendation 2011/696/EU, depending on their specific particle size distribution. For reasons of readability, the Staff Working Paper follows the common practice in using terms for nanomaterials, i.e. when referring to nano-titanium dioxide⁷, the prefix “nano” is not always used, whereas it is used in other cases such as “nanosilver”. However, any numbers such as production tonnages or market values always refer to the total of all nanoforms on the market, unless indicated otherwise.

In chapters 2 to 5, the Staff Working Paper intends to give further explanations on the EU definition of nanomaterial, give an overview of the main types and uses of nanomaterials on the EU market, as well as information on their safety, according to current knowledge available to the Commission, and an overview of issues and activities relating to risk assessment of nanomaterials. In principle, such information can be presented from the perspective of substances at nanoscale, i.e. chemical substances as defined under REACH which are nanomaterials or have forms which are nanomaterials⁸, enumerating their main uses through the supply chain and in final products, or from the perspective of finished products or product areas. In this document, the former approach has been chosen because the number of substances at nanoscale is much more limited than the number of products containing

³ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), OJ L 396, 30.12.2006, p. 1.

⁴ Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, OJ L 353, 31.12.2008, p.1.

⁵ http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/envir/118646.pdf

⁶ OJ L 275, 20.10.2011, p.38.

⁷ i.e. forms of titanium dioxide with more than 50% of particles in the size range 1-100 nm.

⁸ For discussion of the terminology used, see http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/nanomaterials_en.pdf.

nanomaterials and it is therefore easier to present the information in a structured manner. Information on uses in products can be found under each substance heading.

This document can, however, not give a complete or exhaustive picture on all nanomaterial forms or variations of substances. Nanomaterials are often tailored in a very specific way to achieve desired properties. This may alter their behaviour as well as their toxicological and ecotoxicological properties, throughout their life-cycles. In considering the safety of individual forms or variations, care should therefore be taken to properly take into account such variations in combination with specific uses of a particular form, where resulting in different exposure scenarios.

In chapter 6, the Staff Working Paper analyses existing databases on nanomaterials and gives information on a planned European Commission web platform on nanomaterials types and uses, including safety aspects.

2. DEFINITION AND TYPES OF NANOMATERIALS

The Commission adopted on 18 October 2011 Commission Recommendation 2011/696/EU on the definition of Nanomaterial.⁹ The Recommendation responds to the increasing use of specific legislative provisions addressing nanomaterials and the need to ensure harmonised terminology across different pieces of legislation, as well as to a request by the European Parliament.¹⁰

The Recommendation is based on the ISO term “nanomaterial”¹¹, a Reference Report of the European Commission’s Joint Research Centre (JRC)¹², an opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)¹³, on the 195 contributions received during public consultation¹⁴ in October – November 2010, as well as on a number of other sources. The advice is presented in more detail below in chapters 2.2 and 2.3.

The core elements of the definition are laid down in articles 2 to 4:

“2. "Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

3. By derogation from point 2, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

⁹ OJ L 275 20.10.2011 p 38, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF>.

¹⁰ Resolution European Parliament on Regulatory Aspects of Nanomaterials (2008/2208(INI) 24.4.2009.

¹¹ <https://cdb.iso.org/cdb/termentry!display.action?entry=497556&language=1>

¹² <http://ec.europa.eu/dgs/jrc/index.cfm?id=2540>

¹³ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf

¹⁴ <http://ec.europa.eu/environment/consultations/nanomaterials.htm>

4. For the purposes of point (2), "particle", "agglomerate" and "aggregate" are defined as follows:

(a) "Particle" means a minute piece of matter with defined physical boundaries;

(b) "Agglomerate" means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components;

(c) "Aggregate" means a particle comprising of strongly bound or fused particles.”

The purpose of the Recommendation is to ensure consistency across legislative areas as well as across guidance and other technical documents by the European Commission. In addition, the Commission invites Member States, the Union agencies and economic operators to use this definition, for example, in the adoption and implementation of legislation and policy and research programmes concerning products of nanotechnologies

2.1. Application in legislation

The definition will primarily be used in future legislation or in updates of existing legislation to identify materials for which special provisions (concerning for example risk assessment or ingredient labelling) might apply. Those special provisions are not part of the definition but of specific legislation in which the definition will be used. The Recommendation offers a common understanding of the term “nanomaterial” to avoid confusion on terminology and inconsistency between different pieces of legislation. This does not mean that specific legislation needs to apply to all nanomaterials, or that there could not be legislation covering similar materials outside the definition. Since the definition is broad in its coverage, further sector specific qualifiers may be needed in order to identify more precisely those materials that should potentially be subject to specific legislative requirements or policy attention.

For example it is likely that in many cases only materials that are a designed product of a deliberate manufacturing process will be of interest (commonly referred to as "engineered" or "manufactured" nanomaterials). Thus further qualifiers may be added on a case-by-case basis, in order to target the specific materials that qualify for special attention within each regulatory sector.

Another consideration is that in certain specific sectors, like pharmaceuticals, it is established practice to refer to nanoscale being broader than 1 nm – 100 nm. The Recommendation clearly specifies that in such a situation other "nano"-terms may be needed to describe those products.

2.2. Reference Report of the Joint Research Centre

In June 2010 the Joint Research Centre of the European Commission released its Reference Report 'Considerations on a Definition of Nanomaterial for Regulatory Purposes'.¹⁵ The aim of this report was to review and discuss issues and challenges related to a definition of 'nanomaterial', and to provide practical guidance for a definition for regulatory purposes. The report suggests that a definition for regulatory purposes should:

¹⁵ G. Lövestam et al., JRC Reference Report, EUR 24403 EN, ISBN 978-92-79-16014-1, Luxembourg: Publications Office of the European Union, 2010; <http://ec.europa.eu/dgs/jrc/index.cfm?id=2540>.

- only concern particulate nanomaterials,
- be broadly applicable in EU legislation, and in line with other approaches worldwide,
- use size as the only defining property.

2.3. The SCENIHR opinion

The Commission also invited the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to provide scientific input on elements to consider when developing a definition of the term "nanomaterial" for regulatory purposes. The opinion "Scientific basis for the definition of the term 'Nanomaterial'" was adopted on 8 December 2010.¹⁶ SCENIHR concluded that:

- "Whereas physical and chemical properties of materials may change with size, there is no scientific justification for a single upper and lower size limit associated with these changes that can be applied to adequately define **all** nanomaterials.
- There is scientific evidence that no single methodology (or group of tests) can be applied to **all** nanomaterials.
- Size is universally applicable to define all nanomaterials and is the most suitable measurand. Moreover, an understanding of the size distribution of a nanomaterial is essential and the number size distribution is the most relevant consideration.

In order to define an enforceable definition of "nanomaterial" for regulatory use it is proposed to set an upper limit for nanomaterial size and to add to the proposed limit additional guidance (requirements) specific for the intended regulation. Crucial in the guidance that needs to be provided is the extended description of relevant criteria to characterise the nanoscale. Merely defining single upper and lower cut-off limits is not sufficient in view of the size distributions occurring in manufactured nanomaterials.

Alternatively, a tiered approach may be required depending on the amount of information known for any specifically manufactured nanomaterial and its proposed use.

The scientific opinion recognises however that specific circumstances regarding risk assessment for regulatory purposes for certain areas and applications may require the adaptation of any overarching definition.

It should be stressed that 'nanomaterial' is a categorization of a material by the size of its constituent parts. It neither implies a specific risk, nor does it necessarily mean that this material actually has new hazard properties compared to its constituent parts or larger sized counterparts."

2.4. The international context

Several countries, both inside and outside the EU have developed and use working definitions. All these have been carefully scrutinised. There is variability between the different working definitions but most of them are not as precise as the Commission

¹⁶ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf

Recommendation. Most non-EU countries generally use their definitions in a different regulatory context mainly to identify individual materials and/or uses, which then may be subject to specific data provision or risk assessment obligations. In the EU, provisions in individual pieces of legislation (e.g. ingredient labelling, prior notification and authorisation etc.) apply directly to all producers of products containing nanomaterials. Therefore, much more precision is required to provide legal clarity.

Several international organisations have developed their definition of the term nanomaterial. Among these, the definition released by ISO in 2010 (in ISO/TS 80004-1) was developed with the broadest stakeholder base. The approved definition ('material with any external dimension in the nanoscale (2.1) or having internal structure or surface structure in the nanoscale') is fundamentally based on the term 'nanoscale' which was previously defined by ISO (in 2008 in ISO/TS 27687) as 'the size range from approximately 1 nm to 100 nm'.

The ISO definition is used as a working definition for example by the OECD Working Party on Manufactured Nanomaterials (OECD-WPMN). Whilst this broad working definition has proved useful for progressing research and development in this field, it could not be directly used for legal texts, for example due to the approximate nature of the term *nanoscale*.

2.5. Essential elements of the definition

2.5.1. The size range 1 nm – 100 nm

There is no clear scientific justification for setting the thresholds at 1 nm and 100 nm, as specific effects may also occur at a lower and higher size range. On the other hand, particles within the size range of 1 nm to 100 nm may also not show a specific behaviour different from the behaviour of larger particles of the same material. Nevertheless, many of the described specific properties of nanomaterials are actually generated by physics and chemistry within that range.¹⁷ Therefore, in the absence of better arguments for other thresholds, the Commission decided to follow the approach most commonly applied to date, i.e. a size range between 1 nm and 100 nm. This is in line with the advice from SCENIHR and other scientific bodies, as well as with the size range used in the ISO term “nanomaterial”. To make the definition useful for regulatory purposes, it was chosen not to retain the term 'approximately', which qualifies the 1 nm to 100 nm range in the ISO definition.

2.5.2. Aggregates and agglomerates

To some extent, agglomerated or aggregated particles may exhibit the same properties as unbound particles and are therefore covered by the definition. Moreover, there can be cases during the life-cycle of a nanomaterial where the particles are released from weakly bound agglomerates or under certain conditions even from more strongly bound aggregates. The definition in the Recommendation therefore includes particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm - 100 nm.

2.5.3. Based on number of particles, not mass

The amount of nanoparticles in a material can be determined based on their mass fraction (weight of nanoparticles relative to total weight of material) or based on the particle number fractions (number of nanoparticles to total number of particles, "number size distribution").

¹⁷ J. Ramsden, *The nanoscale*, Nanotechnology Perceptions, Vol. 5, p. 3-25 (2008).

Most measurement methods produce an intensity-weighted size distribution (expressing the fractions of particles of a particular size as their relative contribution to the total measured signal intensity). There is a relation between these different size distributions, for every material, but these relations are not usually known and the different size distributions are therefore not directly convertible.

SCENIHR argued in its opinion that "a low mass concentration of nanoparticles in a product may still represent a high number of particles and a mass based distribution can be skewed by the presence of relatively few large and thus heavy particles". As the smallest particles have a proportionally higher specific surface area, which may be relevant for toxicity properties, SCENIHR considered number size distribution as a more relevant metric for possible effects of nanoparticles.

The Commission followed this choice of metrics. Further work is certainly needed on the metrological and standardisation aspects. Previous efforts, for example in the field of fine dust (PM₁₀, PM_{2.5}, etc.), are naturally extending now into the nanoscale. The Commission has already started work to provide practical guidance on particle size measurement methods^{18,19} and quality assurance tools such as interlaboratory studies,^{20,21} nanoparticle reference materials^{22,23,24} for particle size analysis (see also Appendix 9 for further detail), and characterization of complex mixtures of nanoparticles.²⁵

2.5.4. A threshold in the number size distribution

There is no unequivocal scientific basis to suggest a specific threshold in the size distribution below which materials containing particles in the size range 1 nm – 100 nm are not expected to exhibit properties specific to nanomaterials. Because of the proportionally higher specific surface area which may be relevant for toxicity properties exhibited by the smallest particles,

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- ¹⁸ Validation of dynamic light scattering and centrifugal liquid sedimentation methods for nanoparticle characterisation, A. Braun, O. Couteau, K. Franks, V. Kestens, G. Roebben, A. Lamberty, T.P.J. Linsinger, *Advanced Powder Technology*, Vol. 22, p. 766-770 (2010).
- ¹⁹ Measurement of the size of spherical nanoparticles by means of atomic force microscopy, O. Couteau, G. Roebben, *Measurement Science and Technology*, Vol. 22, 065101 (2011).
- ²⁰ Interlaboratory comparison for the measurement of particle size and zeta potential of silica nanoparticles in an aqueous suspension, A. Lamberty, K. Franks, G. Roebben, A. Braun, V. Kestens, T. Linsinger, *Journal of Nanoparticle Research*, Vol.13, p. 7317-7329 (2011).
- ²¹ Interlaboratory Comparison of Size and Surface Charge Measurements on Nanoparticles prior to Biological Impact Assessment, G. Roebben, S. Ramirez-Garcia, V. Hackley, M. Roesslein, F. Klaessig, V. Kestens, I. Lynch, M. C. Garner, A. Rawle, A. Elder, V. Colvin, W. Kreyling, H. Krug, Z. Lewicka, S. McNeil, A. Nel, A. Patri, P. Wick, M. Wiesner, Tian Xia, G. Oberdörster, K. Dawson, *J. Nanoparticle Research*, Vol. 13, p. 2675-2687, (DOI) 10.1007/s11051-011-0423-y (2011).
- ²² Reference materials for measuring the size of nanoparticles, T. P. J. Linsinger, G. Roebben, C. Solans, R. Ramsch, *Trends in Analytical Chemistry*, Vol. 30, p. 18-27 (2011).
- ²³ Certification of equivalent spherical diameters of silica nanoparticles in water, ERM-FD100, A. Braun, K. Franks, V. Kestens, G. Roebben, A. Lamberty, T. Linsinger, Report EUR 24620 EN, European Union, Luxembourg, ISBN 978-92-79-18676-9, 2011.
- ²⁴ Nanoscale reference materials, G. Roebben, G. Reinert, H. Emons, in Nanotechnology Standards, Eds V. Murashov, J. Howard, Springer Science+Business Media, New York, NY, ISBN – 978-1-4419-7852-3 (2011).
- ²⁵ Separation and characterization of gold nanoparticle mixtures by flow-field-flow fractionation, L. Calzolari, D. Gilliland, C. P. Garcia, F. Rossi, *J. Chromatography A*, Vol. 1218, p. 4234 – 4239 (2011).

and following a classic scientific approach to consider three standard deviations, the SCENIHR's advice was to use a threshold value of 0.15 %.

The Commission decided to deviate from this threshold value based on several considerations. Nanoparticles are present in low quantities in most solid materials. The percentage may be significant, in particular in certain powders. Therefore, a threshold of 0.15 % could include too broad a range of materials within the definition, and would have made it difficult to tailor regulatory provisions appropriately.

Nevertheless, in accordance with SCENIHR's advice, even a small number of particles in the range between 1 nm – 100 nm may in certain cases justify a targeted assessment. For such cases, the Recommendation clearly specifies that where warranted by specific concerns for the environment, health, safety or competitiveness a threshold between 1 % and 50 % may be set. These threshold values will be subject to further review by 2014.

2.5.5. The Volume specific surface area

It is possible to measure a specific surface area by mass for dry solid materials or powders with the gas adsorption method (“BET-method”). If the particle density is also known, then the 'volume-specific surface area' can be calculated and used as a proxy to identify a potential nanomaterial. For some materials, there can be a discrepancy between the measurement of the specific surface area and the number size distribution. The measurement of the specific surface area is also sensitive to the measurement method used. It is therefore specified that the results for number size distribution should prevail and it should not be possible to use the specific surface area to demonstrate that a material is not a nanomaterial.

2.5.6. Practical use of the definition

Guidance and standardised measurement methods as well as knowledge about typical concentrations of nanoparticles in representative sets of materials should be developed where feasible and reliable to facilitate the application of the definition in a specific legislative context. The Commission will address these aspects as a matter of priority. However, the use of the definition should not await the outcome of this work and a pragmatic case-by-case approach needs to be applied for the time being. In fact, this should be an iterative process where practical experience will form an important aspect of the further development of measurement methods and standards.

2.5.7. Review of the definition

Some methodological issues and questions of scope could not be fully answered in the preparatory work for the definition. Moreover the nanotechnology sector is rapidly developing and it is therefore expected that the market developments will require the Commission Recommendation to be reviewed at certain intervals. The Recommendation will be reviewed by December 2014.

In view of this review, the Commission services continue to follow up wider work on terms related to nanotechnology and nanomaterials, for example by the International Organization for Standardization (ISO). Details about this work and its relation with the current EU definition are presented in Appendix 1. More information about standardisation work in relation to nanomaterials is given in Appendix 9.

3. OVERVIEW OF NANOMATERIALS, THEIR MARKETS, USES AND BENEFITS

Nanomaterials cover a heterogeneous range of materials. In terms of market volume the main categories on the market include inorganic non-metallic nanomaterials (e.g. synthetic amorphous silica, aluminium oxide, titanium dioxide), carbon based nanomaterials (e.g. carbon black, carbon nanotubes), metal nanoparticles (e.g. nanosilver) and organic, macromolecular or polymeric particulate materials (e.g. dendrimers). Nanomaterials often exist in a variety of forms and may be tailored for individual properties or uses. It was not possible to give market information at such a level of detail, as this information is, if at all, not readily available.

In terms of industrial impact and public exposure the above-mentioned nanomaterials are of immediate regulatory relevance. However, there are also new types of nanomaterials in development, which are often referred to as “second generation” (targeted drug delivery systems, adaptive structures and actuators), “third generation” (novel robotic devices, three-dimensional networks and guided assemblies), and “fourth generation” (molecule-by-molecule design and self-assembly capabilities) nanomaterials.^{26,27,28} However, those are either at research or development stage or at an early stage of market development. Due to the limited available information on those materials, they are not further considered in this Staff Working Paper.

Any estimates of the market size need to be taken with a certain degree of caution, although the general patterns of the estimates (i.e. order of magnitude of tonnage and market value, and relative size of market between the various materials) seem to be rather reliable. According to market data from SRI consulting the global quantity of nanomaterials marketed annually is around 11.5 million tonnes, with a market value of roughly 20 bn €. ²⁹ The market is dominated by two very widespread commodity materials, i.e. carbon black (9.6 million t), and synthetic amorphous silica (1.5 million t). Other nanomaterials with significant amounts on the market include aluminium oxide (200 000 t), barium titanate (15 000 t), titanium dioxide (10 000 t ³⁰), cerium oxide (10 000 t), and zinc oxide (8 000 t). Carbon nanotubes and carbon nanofibres are currently marketed at annual quantities of several hundreds of tonnes (other estimates go up to a few thousands of tonnes). Nanosilver is estimated to be marketed in annual quantities of around 20 tonnes. In addition, there is a wide variety of nanomaterials which are either still at the research and development stage, or which are marketed only in small quantities, mostly for technical and biomedical applications.

The uses of nanomaterials vary substantially, from commodity applications in everyday goods to highly specialised low-volume technical applications, e.g. in electronics or biomedicine. By far the biggest use is as a reinforcing agent for rubber in tyres and other rubber goods (global

²⁶ Roco, M. C. 2004. Nanoscale Science and Engineering: Unifying and Transforming Tools. *AICHE Journal*, 50(5): 890-897.

²⁷ Roco, M. C. 2007. National Nanotechnology Initiative– Past, Present, Future.” In Goddard, W. A., et al. eds. *Handbook on Nanoscience, Engineering and Technology*, Boca Raton, FL, CRC Press; pp. 3.1-3.26.

²⁸ <http://www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf>, p. 12.

²⁹ Stefan Schlag, Bala Suresh, Masahiro Yoneyama and Vivien Yang, <http://www.sriconsulting.com/SCUP/Public/Reports/NANOT000/>; except for carbon black: Chemical Economic Handbook report on carbon black <http://www.sriconsulting.com/CEH/Public/Reports/731.3000/>; Source: IHS Inc. The use of this content was authorized in advance by IHS. Any further use or redistribution of this content is strictly prohibited without written permission by IHS. All rights reserved.

³⁰ The Commission has also received estimates which are higher than this but still in the same rough order of magnitude.

market around 15 bn €, mainly carbon black), followed by functional fillers in polymers (around 1.5 bn €, mainly synthetic amorphous silica, in lower quantities also other metal oxides and silver), various uses in electronics (1 bn €), in cosmetics (100 m €) and biomedical applications (60 m €). In electronics, the biggest use are CMP³¹ slurries, i.e. fine abrasives (mainly colloidal synthetic amorphous silica) used in the preparation of electronic components, followed by multi-layered ceramic capacitors (MLCC, mainly barium titanate). In cosmetics, the main nanomaterials are synthetic amorphous silica, titanium dioxide and zinc oxide. Among biomedical applications, gold nanoparticles in medical diagnostics and silver nanoparticles (e.g. in hospital textiles) seem to be the biggest applications in terms of market value. In addition to those applications, there is use of a wide range of nanomaterials in paints and coatings, catalysts, solar and fuel cells, etc.

The economic sectors with the highest use of nanomaterials³² are aerospace (e.g. lightweight materials, resistant paints and coatings for aerodynamic surfaces); automotive industry and transport (e.g. scratch-resistant paints and coatings, plastics, lubricants, fluids, tyres); agrifood (e.g. sensors to optimise food production); construction (e.g. insulation, stronger building materials, self-cleaning windows); energy generation (e.g. photovoltaics) and storage (e.g. fuel cells and batteries); environment (e.g. soil and groundwater remediation); cosmetics (e.g. sunscreens, tooth paste, face creams); health, medicine and nanobiotechnology (e.g. targeted drug delivery); information and communication technologies, electronics and photonics (e.g. semiconductor chips, new storage devices and displays); security (e.g. sensors to detect biological threats); and textiles (e.g. protective clothing, stronger, self-cleaning or fire resistant fibres).

The benefits of nanomaterials are as diverse as the nanomaterials and their uses. They range from saving lives (e.g. targeted cancer drug delivery) to major technological breakthroughs enabling new applications or reducing the environmental impact of our society (e.g. photovoltaic cells and batteries, light-weight high-strength materials), to improving the function of everyday commodity products (e.g. carbon black in tyres, synthetic amorphous silica in polymers, or as food or cosmetics additive) and to improvements which are mainly of convenience nature (e.g. anti-odour socks).

Nanotechnology has been identified as a key enabling technology (KET) by the High Level Expert Group (HLG) on Key Enabling Technologies.³³ It is highly innovative and provides the basis for further innovation and new products in a wide range of industries, as mentioned above.³⁴ Products underpinned by nanotechnology are forecast to grow from a volume of 200 bn € in 2009 to 2 trn € by 2015.³⁵ These applications will be essential for the competitiveness of a wide area of EU products in the global market. There are also many newly founded

³¹ chemical mechanical planarisation

³² Some of the described uses, e.g. semiconductor chips may relate to nanostructured materials rather than nanomaterials in the sense of the nanomaterial definition.

³³ http://ec.europa.eu/enterprise/sectors/ict/key_technologies/kets_high_level_group_en.htm

³⁴ For a list of effects and property improvements through nanotechnologies see appendix 4.

³⁵ According to Ireland's Nanotechnology Commercialisation Framework 2010 – 2014, Forfas, (Aug.2010) http://www.forfas.ie/media/forfas310810-nanotech_commercialisation_framework_2010-2014.pdf.

http://ec.europa.eu/enterprise/sectors/ict/key_technologies/kets_high_level_group_en.htm; and according to OECD, "Nanotechnology: an overview based on indicators and statistics" (2009), based on Roco, MC and WS Bainbridge, Societal Implications of Nanoscience and Nanotechnology, Kluwer Academic Publ, (2001); both quoted from http://ec.europa.eu/enterprise/sectors/ict/files/kets/hlg_report_final_en.pdf, p.13.

SMEs and spin-off companies in this high technology area. Currently, the direct employment in nanotechnology is estimated at around 300000 to 400000 jobs in the EU.³⁶

In many areas, nanomaterials can significantly contribute to mastering the challenges of the future and the objectives of the EU 2020 Strategy, such as smart growth, developing an economy based on knowledge and innovation, and sustainable growth, promoting a low-carbon, resource-efficient and competitive economy. They can provide essential contributions to green technologies and environmental protection (e.g. sensors for smart electricity grids, filters for drinking water). They can also contribute to inclusive growth by providing new employment and keeping jobs in the EU.

It is difficult to find reliable information on the relative strength of the EU in nanotechnology compared to other regions of the world. The work on this document, in particular Appendix 2, shows that manufacturers and users of nanomaterials are spread all over the industrialised world. Among them are major companies that are located in the EU. The KET HLG report mentions that the EU accounts for 27% of world wide public funding on nanomaterials, 17% of patents³⁷, and 15% of nano-based products.³⁸ To an extent, this may be influenced by the ongoing debate in the EU on regulating nanomaterials. According to a recent survey³⁹, half of the manufacturers and importers of nanomaterials in Europe replying to the survey considered the regulatory uncertainties the most important challenge in bringing nanomaterials on the market. The emerging economies such as the BRIC⁴⁰ countries are still behind the industrialised countries in terms of production and uptake of nanomaterials but are quickly progressing.

4. HEALTH AND SAFETY ASPECTS

Health and safety aspects include possible intrinsic hazard patterns of the nanomaterials, exposure to workers, consumers and at the waste stage, as well as applicable risk management measures. Hazards are determined by the properties of the material itself.⁴¹ However, these hazards will only lead to health or environmental risks⁴² if parts of the human body or the environment are exposed to doses of the nanomaterial which can create harmful effects.

³⁶ http://ec.europa.eu/enterprise/sectors/ict/files/kets/hlg_report_final_en.pdf, p. 13.

³⁷ Source: Cross-sectoral Analysis of the Impact of International Industrial Policy on Key Enabling Technologies (Danish Technological Institute with IDEA Consult, 2011), Institute of Nanotechnology, (analysis from UNU-MERIT and VDI-TZ), 2010, OECD (2009): Nanotechnology: An Overview based on Indicators and Statistics: <http://www.oecd.org/dataoecd/59/9/43179651.pdf>, <http://www.fas.org/sgp/crs/misc/RL34511.pdf>.

³⁸ This figure seems in contradiction to the findings of appendix 2. A possible explanation is that the authors of the work at the basis of the KET reports may have focused on new, technologically innovative applications whereas appendix 2 indicates that by far the highest share of nanomaterial applications is in long established commodity applications, on which the different world regions are likely to have market shares similar to their share in overall economic activities.

³⁹ http://www.gaia.fi/files/680/Study_on_REACH_contribution_to_emerging_technologies_Situation_in_Nanotech_companies_in_Europe_DRAFT.pdf

⁴⁰ Brazil, Russia, China, India

⁴¹ According to Directive 98/24/EC, the term 'hazard' means the intrinsic property of a chemical agent with the potential to cause harm. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:131:0011:0023:EN:PDF>, Article 2(g).

⁴² According to Directive 98/24/EC, the term 'hazard' means the intrinsic property of a chemical agent with the potential to cause harm. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:131:0011:0023:EN:PDF>, Article 2(h).

Correspondingly, risks are determined by a combination of hazards and the probability of exposure.

4.1. Hazard patterns

The hazard patterns vary largely between different nanomaterials. In its opinion of 19 January 2009⁴³, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded: *“The health and environmental hazards were demonstrated for a variety of manufactured nanomaterials. The identified hazards indicate potential toxic effects of nanomaterials for man and environment. However, it should be noted that not all nanomaterials induce toxic effects. Arguably, some manufactured nanomaterials have been in use for a long time (carbon black, TiO₂) and show low toxicity. The 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. As there is not yet a generally applicable paradigm for nanomaterial hazard identification, a case by case approach for the risk assessment of nanomaterials is recommended.”*

In their recent joint report "Impact of Engineered Nanomaterials on Health: Considerations for Benefit-Risk Assessment" EASAC⁴⁴ and the European Commission's Joint Research Centre conclude that *"there is only a limited amount of scientific evidence to suggest that nanomaterials present a risk for human health"*.⁴⁵

Nanomaterials may have a wide range of potential toxic effects, depending on their chemical nature, particle size distribution, particle shape, surface state (e.g. surface area, surface functionalisation, surface treatment), state of aggregation/agglomeration etc. Some of the main known effects from experimental studies are described below and in Appendix 2, under the relevant substance heading. Under experimental conditions, the most common effects observed are a potential to cause oxidative stress and, for some, inflammatory responses or even genotoxic effects.

Like for all chemicals, the potential harmful effects of nanomaterials depend on the doses to which human beings or the environment are exposed to. Typically, experimental data are generated with high doses, identifying effects, and subsequently determining no-effect levels. At low doses, most nanomaterials show little effects in these experiments. Views on whether nanomaterials are hazardous or pose risks diverge, as they depend crucially on whether the experimental data are considered representative for real life conditions.⁴⁶ Some consider that high dose experiments are a normal way of identifying hazards and their results should be an indication of potential risks, whereas others consider that experiments with such high doses are unrealistic and that similar effects could be found at those doses even with very common, non-hazardous substances. Moreover, the route and the conditions under which test animals are exposed to nanomaterials is also critical and subject to substantial methodological

⁴³ http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf, p. 10.

⁴⁴ European Academies Science Advisory Council, <http://www.easac.eu/home.html>

⁴⁵ Impact of Engineered Nanomaterials on Health: Considerations for Benefit-Risk Assessment, Joint EASAC-JRC Report, http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf, p. 8.

⁴⁶ For a discussion of these methodological issues, see e.g. Impact of Engineered Nanomaterials on Health: Considerations for Benefit-Risk Assessment, Joint EASAC-JRC Report, http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf, p. 23.

discussions.⁴⁷ There is however, a consensus on the principle that hazards and risks differ significantly between nanomaterials and that some are hazardous and others are not.

For example, the joint EASAC-JRC report considers that “*Overload conditions especially in the lung (macrophages) have been described for 20 years. It is now well known that overloading the lung with dust particles will severely influence (reduce) the clearance process, thereby prolonging dramatically the biological lifetime of particles within the lung. Eventually, this leads to persistent inflammatory effects with all the characteristics of lung diseases which often end in tumour formation. Therefore, it is recommended that overload conditions should be avoided both in animal studies and for in vitro experiments otherwise excessive doses will generate false-positive results.*

This sense of realism is equally warranted for intended applications where engineered nanomaterials are targeted to the individual in relatively precise amounts. Moreover, testing genotoxicity with overloading concentrations (often cytotoxic concentrations) is also unrealistic as dying cells (apoptosis as well as necrosis) cleave their own DNA, resulting again in false-positive effects⁴⁸. If non-overload conditions are chosen, no carcinogenic effects for such dust particles are found⁴⁹.⁵⁰

There are little epidemiological data, directly evaluating effects of nanomaterials under real life conditions. The few available studies, e.g. on carbon black, are considered as inconclusive because of inconsistent epidemiological evidence.⁵¹ Some other nanomaterials such as synthetic amorphous silica have been on the market for a considerable time, including in high exposure conditions, with little, if any, known adverse health or environmental effects. However, there is also an ever growing variety of new uses and modified forms, for which such experience does not exist. Until understanding is available on the impacts of different forms and modifications of nanomaterials on the hazard patterns, particular care should be taken to avoid undue generalisation of data from one form to another.

In its 2006⁵², 2007⁵³ and 2009⁵⁴ opinions, the SCENIHR acknowledged the possibility that translocation of nanoparticles away from the portal of entry may occur in humans and other species, and that the passage of nanoparticles across membranes could give rise to adverse effects, for example within the cardiovascular system or following passage across the blood – brain barrier.

A number of *in-vivo* studies in rats have demonstrated that certain nanomaterials can penetrate into the body and reach certain organs and tissues (for example in the lung, liver, kidneys, heart, reproductive organs, foetus, brain, spleen, skeleton and soft tissues) via several routes (following inhalation, crossing the pulmonary epithelium and entering the blood stream; or reaching the brain via the olfactory nerve; or crossing the intestinal epithelium after

⁴⁷ Osier M and Oberdörster G 1997, Intratracheal inhalation vs intratracheal instillation: differences in particle effects., *Fundam Appl Toxicol.* 1997 Dec;40(2):220-7.

⁴⁸ Roller, M., *Inhalation Toxicology* **21**, Suppl. 1, 144 (2009).

⁴⁹ Yokohira, M. et al., *Toxicologic Pathology* **36**, 620 (2009).

⁵⁰ Impact of Engineered Nanomaterials on Health: Considerations for Benefit-Risk Assessment, Joint EASAC-JRC Report, http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanoreport-10-11/JRC-EASAC-report.pdf, p. 23.

⁵¹ <http://monographs.iarc.fr/ENG/Monographs/vol93/mono93.pdf>, p. 190.

⁵² http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf

⁵³ http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_012.pdf

⁵⁴ http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf

ingestion).^{55,56,57,58,59,60,61,62,63,64} Moreover, there are open questions on bioaccumulation of nanomaterials and elimination mechanisms from cells and organs.

In animal studies, a whole series of effects have been observed under experimental conditions with high doses (for methodological discussions around such tests, see above). The most important effects have been found in the lungs: there is evidence of inflammation, tissue damage, oxidative stress, chronic toxicity, cytotoxicity, fibrosis, tumours.⁶⁵ Tumour formation was found in rat lungs following intraperitoneal introduction of certain nanomaterials. Furthermore, in long-term studies with intratracheal instillation with nanostructured carbon black, aluminium oxide, aluminium silicate, titanium dioxide (hydrophilic and hydrophobic) and amorphous silicon dioxide, tumours were induced by all of them^{66,67,68,69,70}. Effects like inflammation, fibrosis and tumours were induced by several granular nanomaterials in the lungs after respiratory exposure. Some nanomaterials, including carbon black and titanium

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- ⁵⁵ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.
- ⁵⁶ Kreyling WG, Hirn S, Schleh C. Nanoparticles in the lungs. *Nature Biotechnology* 2010, 28(12):1275-1276.
- ⁵⁷ Kreyling, W. G.; Semmler-Behnke, M.; Seitz, J.; Scymczak, W.; Wenk, A.; Mayer, P.; Takenaka, S.; Oberdorster, G., Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. *Inhalation Toxicology* 2009, 21, (S1), 55-60.
- ⁵⁸ Semmler-Behnke, M.; Kreyling, W.; Lipka, J.; Fertsch, S.; Wenk, A.; Takenaka, S.; Schmid, G.; Brandau, W., Biodistribution of 1.4- and 18-nm Gold Particles in Rats. *Small* 2008, 4, (12), 2108-2111.
- ⁵⁹ Semmler, M.; Seitz, J.; Erbe, F.; Mayer, P.; Heyder, J.; Oberdorster, G.; Kreyling, W. G., Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. *Inhalation Toxicology* 2004, 16, (6-7), 453-9.
- ⁶⁰ Kreyling, W. G.; Semmler, M.; Erbe, F.; Mayer, P.; Takenaka, S.; Schulz, H.; Oberdörster, G.; Ziesenis, A., Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *Journal of Toxicology and Environmental Health-Part A* 2002, 65, (20), 1513-1530.
- ⁶¹ Yu, L. E., Yung, L.-Y. L., Ong, C.-N., Tan, Y.-L., Balasubramaniam, K. S., Hartono, D., Shui, G., Wenk, M. R., Ong, W.-Y., 'Translocation and effects of gold nanoparticles after inhalation exposure in rats', *Nanotoxicology*, 1, 2007, pp. 235-242.
- ⁶² AFSSET – Agence Française de Sécurité Sanitaire de l'Environnement et du Travail, *Les nanomatériaux. Sécurité au travail*, 2008. Available at: <http://www.afsset.fr/upload/bibliotheque/258113599692706655310496991596/afsset-nanomateriaux-2-avis-rapport-annexes-vdef.pdf>.
- ⁶³ Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J.N. & Oberdörster, G., 'Translocation of inhaled ultrafine manganese oxide particles to the central nervous system', *Environ Health Perspect*, 114, 2006, pp. 1172-1178.
- ⁶⁴ Oberdörster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W. & Cox, C., 'Translocation of inhaled ultrafine particles to the brain', *Inhalation Toxicology*, 16, 2004, pp. 437-445.
- ⁶⁵ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.
- ⁶⁶ Mohr, U., Ernst, H., Roller, M., Pott, F., 'Pulmonary tumor types induced in Wistar rats of the so called „19-dust study“', *Exp Toxicol Pathol*, 58, 2006, 13-2.
- ⁶⁷ Roller, M., Pott, F., 'Lung tumor risk estimates from rat studies with not specifically toxic granular dusts', *Ann. N. Y. Acad. Sci.*, 2006, 266-280.
- ⁶⁸ Pott, F., Roller, M., 'Lung tumours in rats after intratracheal instillation of dusts', *Ann Occup Hyg*, 38, 1994, 357-363.
- ⁶⁹ Pott, F., Roller, M., 'Carcinogenicity study with nineteen granular dusts in rats', *Eur. J. Oncol.*, 10, 2005, 249-281.
- ⁷⁰ Dasenbrock, C., Peters, L., Creutzenberg, O., Heinrich, U., 'The carcinogenic potency of carbon particles with and without PAH after repeated intratracheal administration in the rat', *Toxicol Lett*, 88, 1996, 15-21.

dioxide, were on the basis of experimental animal studies classified as “possibly carcinogen to humans” (group 2B) by IARC.⁷¹

In particular, carbon nanotubes (CNTs) of length, diameter and rigidity ratios comparable to those of toxic forms of asbestos were shown to have a potential under experimental conditions to induce effects similar to those of asbestos.⁷² There is no clear evidence of acute effects in other organs than lungs but chronic exposure may lead to elevated accumulation of translocated nanomaterials eventually leading to adverse health effects.^{73,74,75,76,77} In particular, in case of respiratory exposure to nanomaterials special attention is to be given to the cardio-vascular system as natural ambient particles and incidental ultrafine particles (e.g. welding fumes and combustion products) show some similarities (poor solubility, persistence in the lungs) that might indicate some common properties.^{78,79,80,81,82,83}

Extensive data⁸⁴ on adverse effects of particles of different sizes in ambient and indoor air can also contribute to the understanding of the safety aspects of nanomaterials in certain

⁷¹ <http://monographs.iarc.fr/ENG/Monographs/vol93/index.php>

⁷² Donaldson, K., Murphy, F. A., Duffin, R., Poland, C. A., 'Asbestos, carbon nanotubes and the pleural mesothelium: a review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma', *Particle & Fibre Toxicology*, Vol. 7, p. 5, 2010.

⁷³ Kreyling WG, Hirn S, Schleh C. Nanoparticles in the lungs. *Nature Biotechnology* 2010, 28(12):1275-1276.

⁷⁴ Kreyling, W. G.; Semmler-Behnke, M.; Seitz, J.; Scymczak, W.; Wenk, A.; Mayer, P.; Takenaka, S.; Oberdorster, G., Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. *Inhalation Toxicology* 2009, 21, (S1), 55-60.

⁷⁵ Semmler-Behnke, M.; Kreyling, W.; Lipka, J.; Fertsch, S.; Wenk, A.; Takenaka, S.; Schmid, G.; Brandau, W., Biodistribution of 1.4- and 18-nm Gold Particles in Rats. *Small* 2008, 4, (12), 2108-2111.

⁷⁶ Semmler, M.; Seitz, J.; Erbe, F.; Mayer, P.; Heyder, J.; Oberdorster, G.; Kreyling, W. G., Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. *Inhalation Toxicology* 2004, 16, (6-7), 453-9.

⁷⁷ Kreyling, W. G.; Semmler, M.; Erbe, F.; Mayer, P.; Takenaka, S.; Schulz, H.; Oberdorster, G.; Ziesenis, A., Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *Journal of Toxicology and Environmental Health-Part A* 2002, 65, (20), 1513-1530.

⁷⁸ Kreyling WG, Hirn S, Schleh C. Nanoparticles in the lungs. *Nature Biotechnology* 2010, 28(12):1275-1276.

⁷⁹ Kreyling, W. G.; Semmler-Behnke, M.; Seitz, J.; Scymczak, W.; Wenk, A.; Mayer, P.; Takenaka, S.; Oberdorster, G., Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. *Inhalation Toxicology* 2009, 21, (S1), 55-60.

⁸⁰ Semmler-Behnke, M.; Kreyling, W.; Lipka, J.; Fertsch, S.; Wenk, A.; Takenaka, S.; Schmid, G.; Brandau, W., Biodistribution of 1.4- and 18-nm Gold Particles in Rats. *Small* 2008, 4, (12), 2108-2111.

⁸¹ Semmler, M.; Seitz, J.; Erbe, F.; Mayer, P.; Heyder, J.; Oberdorster, G.; Kreyling, W. G., Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. *Inhalation Toxicology* 2004, 16, (6-7), 453-9.

⁸² Kreyling, W. G.; Semmler, M.; Erbe, F.; Mayer, P.; Takenaka, S.; Schulz, H.; Oberdorster, G.; Ziesenis, A., Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *Journal of Toxicology and Environmental Health-Part A* 2002, 65, (20), 1513-1530.

⁸³ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.

⁸⁴ Last WHO systematic review for regulatory purposes: <http://www.euro.who.int/en/what-we-do/health-topics/environment-and-health/air-quality/publications/pre2009/health-aspects-of-air-pollution-results-from-the-who-project-systematic-review-of-health-aspects-of-air-pollution-in-europe>. Update preparation in progress as part of ongoing review of Directive on ambient air quality 2008/50/EC. On indoor air quality see <http://www.envie-iaq.eu/>.

circumstances, in particular epidemiological and toxicological studies addressing ultrafine particles.^{85,86,87} Ultrafine particles are present in our everyday lives and at various conventional workplaces, generated by the applied work processes (i.e. work processes generating ultrafine dust, aerosols or fumes, such as spraying, dry-cutting, polishing, material processing with laser applications, combustion processes, welding processes generating metal-welding fumes, etc.).^{88,89,90} Diesel exhaust exposure and PM10 concentrations have been related to higher mortality in the general population at higher pollution rates, and to aggravation of asthma and lung cancer in workers.⁹¹ Fine particulate matter exposures have also been linked to cardiovascular effects.^{92,93} Metal oxide fumes, for example by welding, casting and abrasive treatment, may lead to metal fume fever and more severe irreversible respiratory illness.⁹⁴ There are continuous gaps in knowledge in relation to health effects of individual components of particulate matter.⁹⁵ There is major ongoing research on the health impact of particulate matter, including in particular transport-related particles, on human health.⁹⁶ A significant body of EU environmental regulation including emission standards⁹⁷ and workplace codes of practice or regulations have been designed to limit exposure to particulate matter.⁹⁸

Catalytic effects and the risk of fire or explosion should be taken into account in the risk assessment of handling powders consisting of nanomaterials (nanopowders), in particular metal nanopowders.⁹⁹

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- ⁸⁵ Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect.* 2005 Jul;113(7):823-39.
- ⁸⁶ Cassee F, Mills N, Newby D: Cardiovascular Effects of Inhaled Ultrafine and Nano-Sized Particles, Wiley (2011).
- ⁸⁷ Hoek G et al: Concentration Response Functions for Ultrafine Particles and All-Cause Mortality and Hospital Admissions: Results of a European Expert Panel. *Environ. Sci. Technol.* 2010, 44, 476–482 Elicitation.
- ⁸⁸ Vorkommen ultrafeiner Aerosole am Arbeitsplatz, Möhlmann C.. Available at http://www.dguv.de/ifa/de/pub/grl/pdf/2005_196.pdf.
- ⁸⁹ Riediger, G; Möhlmann, C.: Ultrafeine Aerosole an Arbeitsplätzen - Konventionen und Beispiele aus der Praxis. *Gefahrstoffe - Reinhalt. Luft* 61 (2001) Nr. 10, S. 429-434.
- ⁹⁰ Ultrafine aerosols at workplaces (BIA-Report 7/2003e). available at: <http://www.dguv.de/ifa/en/pub/rep/pdf/rep04/biar0703e/bia0603e.pdf>.
- ⁹¹ Scientific Basis for Swedish Occupational Standards xxiv, *Arbete och Hälsa*, National Institute for Working Life 2003. Available at http://www.inchem.org/documents/kemi/kemi/ah2003_16.pdf.
- ⁹² Fang, S., Cassidy, A., Christiani, D., A Systematic Review of Occupational Exposure to Particulate Matter and Cardiovascular Disease. *Int J Environ Res Public Health.* 2010 April; 7(4): 1773–1806.
- ⁹³ Morawska, L., Health Impacts of Ultrafine Particles, Australian Government Department of the Environment and Heritage 2004. Available at <http://www.environment.gov.au/atmosphere/airquality/publications/health-impacts/pubs/content-chapters1-4.pdf>.
- ⁹⁴ Deaths from pneumonia after welding, *Scand J Work Environ Health* 2001;27(5):353 and Kaye P, Young H, O'Sullivan I (May 2002). "Metal fume fever: a case report and review of the literature". *Emerg Med J* 19 (3): 268–9.
- ⁹⁵ Bell M: Assessment of the Health Impacts of Particulate Matter Characteristics; HEI Research Report #161 (2012). www.escapeproject.eu; <http://www.transphorm.eu/>.
- ⁹⁶ http://ec.europa.eu/environment/air/index_en.htm
- ⁹⁷ For example Technical Rules for Hazardous Substances TRGS 528, Welding Work, available at <http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/TRGS-528.pdf?blob=publicationFile&v=2>.
- ⁹⁸ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.

There is a number of experimental studies on ecotoxicity of nanomaterials which show varying results and a variety of ecotoxic effects. For example Zhu et al¹⁰⁰ report reduced length and body weights of fish as a result of exposure to fullerene aggregates. Silver and copper nanoparticles are known to be strongly ecotoxic. There are indications that this is primarily related to ion release (which is relatively high compared to bigger particles due to the larger specific surface) rather than to the particles themselves. There are also many studies on titanium dioxide and zinc oxide, showing diverging results, depending on the forms of nanoparticles studied.¹⁰¹ Unfortunately, those forms were often inadequately characterized to enable the results from these studies to be extrapolated to other circumstances. Overall, the level of ecotoxicological knowledge is significantly lower than the level of toxicological knowledge. There are many uncertainties relating to simulation of environmental conditions in experiments (usually much higher concentration and more short-term exposure than realistic environmental conditions, interferences through solvents, strong dependence on forms of nanoparticles, surface treatment etc.). There are also open questions on bioaccumulation and long term exposure, even though this does not seem to be a general issue for all nanomaterials, as shown by the long presence of certain nanomaterials on the market, and the absence of observed effects for these nanomaterials.

Although it is not always possible to identify which information in REACH registration dossiers relates to or covers the nanoform(s), it should be noted that most of the substances registered under REACH which have nanoforms have not been classified by the registrants for any hazard endpoint.¹⁰²

In **conclusion**, toxicological knowledge about nanomaterials is improving continuously. Despite the open questions described above, available toxicological knowledge on nanomaterials suggests that many nanomaterials are non-hazardous at moderate doses while others are hazardous. There is a need for a more focused risk assessment of nanomaterials, on a case-by-case basis. This should allow identifying risks related to specific nanomaterials and their uses, and taking appropriate risk management measures. In the absence of more detailed knowledge, there is a need to apply precautionary considerations to reduce exposure, in particular at the workplace. Workplace exposure should be reduced to the minimum applying the hierarchy of control measures according to the workplace legislation such as Directive 98/24/EC and specific guidance from the OECD (see 4.2). and, where these would not be possible because of insufficient scientific information for the necessary hazard and/or risk characterisation, applying the ALARA¹⁰³ principle on the workplace exposure to ensure the safe use of nanomaterials in other ways.

Moreover, this also does not preclude that additional precautionary action such as substance or use restrictions for individual substances (including on particular forms or modifications of nanomaterials) may become necessary if new information becomes available indicating serious potential risks. Scientific work to inform the risk assessments process should continue, especially regarding nanomaterials for which initial information suggests possible serious

¹⁰⁰ Zhu, X.S., Zhu, L., Lang, Y.P. and Chen, Y.S. 2008: Oxidative stress and growth inhibition in the freshwater fish *Carassius auratus* induced by chronic exposure to sublethal fullerene aggregates, *Environmental Toxicology and Chemistry*, vol. 27, no. 9, pp. 1979-1985.

¹⁰¹ Reviewed in: Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enrhres-final-report>; conclusions on p. 359 – 360.

¹⁰² For details, see appendix 2. It should be noted that most (though not all) of the registrations for the concerned substances are unspecific with respect to the nanoforms.

¹⁰³ As Low As Reasonably Achievable

hazards, and for developing a better understanding of the role of different forms and modifications of nanomaterials in generating specific hazard patterns.

4.2. Exposure patterns

There are very few measured data on exposure to nanomaterials and available exposure models. Therefore, exposure aspects can be mainly addressed through general considerations and assumptions in exposure scenarios. One known important factor to characterise exposure is whether nanoparticles occur as free particles, whether they occur in aggregates or agglomerates, whether they are bound in a matrix or enclosed in equipment, or whether they are transformed during the production process in a way that they do not occur as nanoparticles in the finished product.

Exposure is likely to be most serious if particles occur in free form, although this seems to be relatively rare. Often, nanoparticles aggregate or agglomerate under normal environmental conditions, thereby changing (but not necessarily losing) their nanospecific properties. Studies are investigating whether, once inhaled and in lung fluid, such aggregates/agglomerates could de-aggregate/de-agglomerate and nanoparticles could be released.^{104,105} There can be cases during the life-cycle of a nanomaterial where the particles are released from weakly bound agglomerates or under certain, perhaps rather unlikely, conditions even from more strongly bound aggregates. Exposure is less likely if nanomaterials are bound in a matrix or enclosed in equipment. It may still occur in the long term, through environmental degradation or at the waste stage, or during specific operations such as abrasion or machining of the matrix. This may also have impacts on the environment and indirectly on humans (e.g. through drinking water or air), though the evidence is still very limited and controversial.^{106,107} Generally, the highest risk of exposure to nanomaterials is to workers at the production stage, although this is also where exposure is generally best controlled with the use of closed systems.¹⁰⁸ Nevertheless, risks of exposure during maintenance and cleaning of such closed systems, as well as in the case of leakage have to be considered. Measurements of airborne nanomaterials have shown higher levels where processes such as extrusion and cutting of bags containing nanomaterials, or dry-sawing of nanomaterial-containing composites took place.¹⁰⁹ The risk

¹⁰⁴ Meißner, T., Potthoff, A. & Richter, V., 'Physico-chemical characterization in the light of toxicological effects', *Inhalation Toxicology*, 21.s1, 2009, pp. 35-39.

¹⁰⁵ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.

¹⁰⁶ <http://www.nanex-project.eu/index.php/public-documents>

¹⁰⁷ OECD-WPMN Report of the Workshop on Risk Assessment of Manufactured Nanomaterials in a regulatory context, held on 16-18 September 2009, in Washington D.C., United States: No. 21 - ENV/JM/MONO(2010)10.

¹⁰⁸ OECD-WPMN Guidance on exposure assessment and mitigation: No. 28 - ENV/JM/MONO(2010)47 Compilation and Comparison of Guidelines Related to Exposure to Nanomaterials in Laboratories; No. 13 - ENV/JM/MONO(2009)18 Report of an OECD Workshop on Exposure Assessment and Exposure Mitigation: Manufactured Nanomaterials; No. 12 - ENV/JM/MONO(2009)17 Comparison of Guidance on Selection of Skin Protective Equipment and Respirators for Use in the Workplace: Manufactured Nanomaterials; No. 11 - ENV/JM/MONO(2009)16 Emission Assessment for Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance; No. 10 - ENV/JM/MONO(2009)15 Identification, Compilation and Analysis of Guidance Information for Exposure Measurement and Exposure Mitigation: Manufactured Nanomaterials; No. 8 - ENV/JM/MONO(2009)6 Preliminary Analysis of Exposure Measurement and Exposure Mitigation in Occupational Settings: Manufactured Nanomaterials.

¹⁰⁹ Möhlmann, C. et al., "Exposure to carbon nano-objects in research and industry", INRS Occupational Health Research Conference 2011 "Risks associated with nanoparticles and nanomaterials", April 2011,

of chronic exposure of workers to situations where such nanomaterials-containing products are processed (e.g. polishing) requires further investigation.

Although there are very little measured data, it seems quite obvious that exposure at the use stage varies strongly, depending on the type of application. In technical applications where the nanomaterials are bound in a matrix (e.g. paints or construction materials) or embedded in equipment parts (e.g. in electronics), exposure during use is estimated to be relatively low. Exceptions might be when such matrices are for example abraded or machined (e.g. dry-sawed).¹¹⁰ In general, little or no information is currently available in the Safety Data Sheets (SDS)^{111,112,113,114}, making it often difficult for employers and workers at the use stage to assess specific exposure to nanomaterials and to implement adequate prevention measures. Relevant changes in REACH Annex II, which is the legal framework for Safety Data Sheets, have been made recently¹¹⁵, and the recent guidance from ECHA on the Safety Data Sheets gives further advice on how to address characteristics of nanomaterials.¹¹⁶ There are ongoing discussions whether leaching (e.g. of outdoor paints or release at the end-of-life) could lead to the release of significant amounts of nanoparticles. In other applications such as in food and cosmetics, exposure is estimated to be high due to ingestion or direct contact with the skin. In between there are applications such as tyres, where a certain degree of wear and thus environmental exposure occurs.

Exposure to nanomaterials may also occur at the waste stage. Although still controversial and subject to debate, there are results from studies on grinding of materials consisting of nanomaterials bound in a common matrix¹¹⁷ which do not confirm that those nanoparticles are released from the matrix during grinding (like in any fine grinding process, there can be release of nanoparticles but these are also formed in a similar way from the matrix in which the bound nanoparticles are embedded or from matrices which do not contain any nanomaterials at all). However, fine airborne particles containing manufactured nanoparticles

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- Conference proceedings, Session II, p. 64, [http://en.inrs.fr/inrs-pub/inrs01.nsf/IntranetObject-accesParReference/Pdf%20EN_Nano2011_Abstracts/\\$File/EN_Nano2011_Abstracts.pdf](http://en.inrs.fr/inrs-pub/inrs01.nsf/IntranetObject-accesParReference/Pdf%20EN_Nano2011_Abstracts/$File/EN_Nano2011_Abstracts.pdf).
- ¹¹⁰ Möhlmann, C. et al., "Exposure to carbon nano-objects in research and industry", INRS Occupational Health Research Conference 2011 "Risks associated with nanoparticles and nanomaterials", April 2011, Conference proceedings, Session II, p. 64.
- ¹¹¹ Schneider, T., Jansson, A., Jensen, K. A., Kristjansson, V., Luotamo, M., Nygren, O., Skaug, V., Thomassen, Y., Tossavainen, A., Tuomi, T., Wallin, H., *Evaluation and control of occupational health risks from nanoparticles*, TemaNord 2007:581, Nordic Council of Ministers, Copenhagen, 2007. Available at: http://www.norden.org/da/publikationer/publikationer/2007-581/at_download/publicationfile.
- ¹¹² Borm, P., Houba, R., Linker, F., *Good uses of nanomaterials in the Netherlands*, 2008. Available at: <http://www.nano4all.nl/Reporshortsummary.pdf>.
- ¹¹³ ACLI - Austrian Central Labour Inspectorate, *Use of Nano at the Workplace*, 2009. Available at: http://www.arbeitsinspektion.gv.at/NR/rdonlyres/592E7E96-E136-453F-A87B-3C393FC039E1/0/Nano_Untersuchung.pdf.
- ¹¹⁴ SafeWork Australia, *An Evaluation of MSDS and Labels associated with the use of Engineered Nanomaterials*. Available at <http://safeworkaustralia.gov.au/AboutSafeWorkAustralia/Whatwedo/Publications/Pages/RP201006EvaluationOfMSDSAndLabels.aspx>.
- ¹¹⁵ Commission Regulation (EU) No 453/2010 of 20 May 2010 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Autorisation and Restriction of Chemicals (REACH), OJ L 133, 31.5.2010, p. 1.
- ¹¹⁶ http://echa.europa.eu/documents/10162/17235/sds_en.pdf
- ¹¹⁷ E.g. D. Göhler, M. Stintz, L. Hillemann and M. Vorbau: Characterization of Nanoparticle Release from Surface Coatings by the Simulation of a Sanding Process. *Ann. Occup. Hyg.*, Vol. 54, No. 6, pp. 615–624, 2010.

could be inhaled and thus could possibly serve as a “vehicle” transporting nanomaterials into the body. Studies are investigating whether, once in the body, such bound nanomaterials could be released (for example in lung fluid) or would influence the toxicity of the fine particles.^{118,119}

There are few studies on the environmental fate and behaviour of nanomaterials. This is mainly due to a lack of methods to detect nanoparticles in the environment. A particular problem is the distinction between manufactured nanoparticles and incidental or natural nanoparticles. Even under workplace conditions, the background level in airborne nanoparticles (e.g. through diesel exhaust nanoparticles) may dominate over additions through emissions from the manufacturing process. Apart from clear indications that nanoparticles interact with natural organic matter, there is also little information about the fate of nanoparticles in the aquatic environment.

In addition, there may also be exposure to nanomaterials as a result of their presence in recycled materials. While there is no information available on any identified adverse effects to date, the issue is starting to be considered.^{120,121,122}

In conclusion, much more work on developing exposure data and detection methods for nanomaterials in the environment is needed.

4.3. Risk characterisation

Mainly as a result of the lack of exposure data¹²³, risk characterisation and combining hazard and exposure data necessarily remains at a very preliminary and qualitative level. As long as the considered nanomaterials are non-hazardous and do not bio-accumulate, this is a limited problem, as exposure to such materials is unlikely to cause toxic and ecotoxic effects, at least at moderate doses. Where exposure is unlikely to occur, either because nanomaterials are strictly contained or embedded in a matrix, or as a result of risk management measures, this will also be a limited problem. Therefore, the focus of attention of the regulators should be those nanomaterials for which initial information suggests possible hazards or bioaccumulation and the applications of these nanomaterials where significant exposure of workers, consumers or the environment may occur.

According to current knowledge, examples of such nanomaterials are the different forms of nano-titanium dioxide and nano-zinc oxide (due to high potential exposure, in particular in their applications as UV-filters), carbon nanotubes (for the possible carcinogenicity of certain forms) and nano-silver (for possible ecotoxicity).

¹¹⁸ Meißner, T., Potthoff, A. & Richter, V., ‘Physico-chemical characterization in the light of toxicological effects’, *Inhalation Toxicology*, 21.s1, 2009, pp. 35-39.

¹¹⁹ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view

¹²⁰ (Sachverständigenrat 2011) Vorsorgestrategien für Nanomaterialien, Sondergutachtendes Sachverständigenrats für Umweltfragen, Berlin 2011 http://www.umweltrat.de/SharedDocs/Downloads/DE/02_Sondergutachten/2011_09_SG_Vorsorgestrategie%20f%C3%BCr%20Nanomaterialien.pdf?__blob=publicationFile

¹²¹ (Swiss Government 2008) Action Plan “Synthetic Nanomaterials” of the Swiss Government, Bern 2008; <http://www.bafu.admin.ch/publikationen/publikation/00574/index.html?lang=en>

¹²² OECD Working Party on Resource Productivity and Waste, Meeting 15-16 February 2012

¹²³ This is without prejudice to many gaps in hazard data. However, in this context, the almost general absence of exposure data makes risk characterisation systematically difficult.

However, priorities will need to be reviewed depending on the outcome of this work and on new scientific and market developments. In particular in emerging uses, hazard patterns of nanomaterials may be different from studied forms, including through modification by downstream users of nanomaterials. Exposure patterns of nanomaterials may change with their uptake in specific new applications. Therefore, care must be taken that those trends are adequately reflected in risk assessments, including exposure scenarios.

4.4. Risk management

There is a variety of possible risk management measures to avoid exposure, in particular at the workplace. Prevention of occupational risks is an employer's responsibility according to Directive 89/391/EEC on the introduction of measures to encourage improvements in the safety and health of workers at work.¹²⁴ In situations where elimination of the risk or substitution by a substance less hazardous are not possible, the hierarchy of control measures as provided for by Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work¹²⁵ gives priority to reduction of the risk at source. Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work¹²⁶ introduces more stringent provisions in the case of carcinogen or mutagen substances, for example regarding substitution. These risk management measures include, as also for traditional chemicals, process control (e.g. various degrees of containment, applying work processes where nanomaterials are in a fluid matrix instead of in the powder form), local ventilation and discharge control measures (e.g. filtration), organisational measures (reducing the number of workers exposed, reducing the exposure time, etc.) and, as last resort, personal protective equipment. The risks of exposure due to technical problems (damage, poor tightness) of the containment systems as well during maintenance and cleaning operations have to be considered. An overview of relevant literature on workplace exposure to nanoparticles, on risk communication on nanomaterials in the workplace, as well as company Good Practice examples on the risk management of nanomaterials¹²⁷ has been compiled by the European Agency for Safety and Health at Work (EU-OSHA). An updated list of major information sources with regard to occupational safety and health (OSH) and nanomaterials, including examples of risk assessment tools and guidance developed in EU Member States is included in Appendix 6. By end 2012, EU-OSHA will make a web portal dedicated to OSH and nanomaterials containing information material for workplaces available on its website.¹²⁸

A tiered pragmatic approach to exposure measurements and assessment of nanoscale aerosols for workplace operations was recently developed in Germany in a dialogue between a number

¹²⁴ OJ L 183, 29.6.1989, p. 1-8; http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31989L0391&model=guichett.

¹²⁵ OJ L 131, 5.5.1998, p. 11-23; http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31998L0024&model=guichett.

¹²⁶ OJ L 229, 29.6.2004, p.23; <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:229:0023:0034:EN:PDF>.

¹²⁷ http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view; http://osha.europa.eu/en/publications/literature_reviews/risk-perception-and-risk-communication-with-regard-to-nanomaterials-in-the-workplace/view; and http://osha.europa.eu/en/practical-solutions/case-studies/index_html/practical-solution?SearchableText=&is_search_expanded=True&getRemoteLanguage=en&keywords%3Alist=nanotechnology&nace%3Adefault=&multilingual_thesaurus%3Adefault=&submit=Search

¹²⁸ <http://osha.europa.eu>

of institutions.¹²⁹ The approach combines established risk management concepts with elements of exposure assessment according to the current technology, and it is based on the experience of the participating practitioners.

In order to better understand and improve the knowledge base on protection of workers from possible risks arising from exposure to and use of nanomaterials and/or nanotechnology in the workplace, the Commission has launched a study¹³⁰ aiming to: **(i)** check the extent to which the current EU OSH legal framework covers sufficiently and effectively nano-related risks in the workplace; **(ii)** delineate a series of possible scenarios that should help shed light on which options may be better suited to tackling nano-related workplace risks without undue demands on businesses; and **(iii)** the drafting of a practical guidance document that may help tackle the mentioned workplace risks in waiting for a developed regulatory framework to be put in place. To achieve this, the study will include an in-depth characterisation of likely exposures of workers to nanomaterials, relevant risk assessment issues, types and effectiveness of risk management measures and relevant regulatory issues. The study is scheduled to be finalised by early 2013. The Commission will also give consideration to requesting a more robust involvement of the EU-OSHA with a view to raise awareness and/or disseminate information, as appropriate, in relation to any possible risks posed by nanomaterials and/or nanotechnology in EU workplaces.

Awaiting the outcome of this study, new approaches aiming to control workers exposure have recently been presented. An example is the so-called Nano Reference Values (NRVs) system¹³¹ proposed as provisional alternatives for HBR-OELs¹³² or DNELs¹³³ or US-NIOSH's approach in recommending an OEL for TiO₂ nanoparticles.¹³⁴ This system is based on a precautionary, thus not on a risk-based approach. While not guaranteeing that exposures below the NRV-level are safe, NRVs define a maximum generic level for the concentration of nanoparticles in the workplace atmosphere, corrected for the background particle concentration. NRVs are intended to be a warning level to urge for risk management of nanoparticles at the workplace. According to this approach, when exceeding this level of exposure, reducing measures should be taken. In any event such measures should also be considered for exposures below the NRVs.

Exposure to consumers and the environment at the use stage, and to an extent also at the waste stage is more difficult and often impossible to control through risk management measures at the place of exposure. There are in principle many tools to manage risks for consumers and the environment at the place of exposure such as proper use instructions, disposal or recycling of products.¹³⁵ Nevertheless, as they are not always effective, the most

¹²⁹ <https://www.vci.de/Downloads/Tiered-Approach.pdf>

¹³⁰ Study service contract to establish the potential impact of Nanomaterials & Nanotechnology at the Workplace, evaluate the scope and requirements of possible modifications of relevant EU Safety & Health at Work legislation and elaborate a guidance document to accommodate corresponding risks/concerns, with a view to ultimately ensure adequate protection of workers health and safety from risks inherent to exposure to Nanomaterials and/or Nanotechnology use.

¹³¹ As currently developed and tested under the auspices of the IVAM University of Amsterdam, the Dutch Trade Unions and Dutch Employers Organization.

¹³² health-based recommended occupational exposure limit

¹³³ derived no-effect level

¹³⁴ NIOSH Occupational Exposure to Titanium Dioxide, Current Intelligence Bulletin 63, 2011 (<http://www.cdc.gov/niosh/docs/2011-160/>) with NIOSH's OEL recommendation of 0.3 mg/m³ for nanoparticles of TiO₂ (versus 2.4 mg/m³ for fine particles >100nm).

¹³⁵ See http://ec.europa.eu/environment/index_en.htm

realistic and promising approach to control exposure to consumers and the environment, where needed, remains the reduction of emissions at source.

In conclusion, where risks are identified, appropriate risk management measures need to be taken. This includes a range of possible measures to control exposure at the workplace or minimize exposure to consumers and the environment through risk management measures at source, and to the extent possible through measures such as proper use instructions, disposal or recycling of products. Where the application of current regulatory obligations such as from REACH registration or the Chemical Agents Directive may not be sufficiently effective, further regulatory action, including possible restrictions of use of certain nanomaterials may become necessary.

5. RISK ASSESSMENT

5.1. The opinions of the EU risk assessment bodies

In light of the benefits derived from applications of the nanotechnologies and resulting, expected growth of their presence on the EU market, following an initial mapping of the potential risks of nanotechnologies in March 2004¹³⁶, the European Commission asked, respectively, the three non-food Scientific Committees (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS), Scientific Committee on Health and Environmental Risks (SCHER))¹³⁷, the European Food Safety Authority (EFSA)¹³⁸, the European Medicines Agency (EMA)¹³⁹, and the European Chemicals Agency (ECHA)¹⁴⁰ to address the safety of nanomaterials.

SCENIHR concluded that “while risk assessment methodologies for the evaluation of potential risks of substances and conventional materials to man and the environment are widely used and are generally applicable to nanomaterials, specific aspects related to nanomaterials still require further development. This will remain so until there is sufficient scientific information available to characterise the harmful effects of nanomaterials on humans and the environment.”¹⁴¹

The guidance provided by EFSA (2011)¹⁴² offers a strategy for risk assessment in food and feed. It concerns (i) characterisation requirements of engineered nanomaterials used in food and feed and (ii) testing approaches to identify and characterise hazards to human health during use. The guidance lowers information requirements in the absence of exposure, i.e., no migration from a food contact material, or of absorption of engineered nanomaterials as such because of complete degradation/dissolution. The guidance also flags uncertainties.

¹³⁶ http://ec.europa.eu/health/ph_risk/documents/ev_20040301_en.pdf

¹³⁷ http://ec.europa.eu/health/scientific_committees/policy/index_en.htm

¹³⁸ <http://www.efsa.europa.eu/>

¹³⁹ <http://www.ema.europa.eu/>

¹⁴⁰ http://echa.europa.eu/home_en.asp

¹⁴¹ Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion on: Risk Assessment of Products of nanotechnologies. Adopted by the SCENIHR during the 28th plenary meeting of 19 January 2009. (http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf), p. 52.

¹⁴² Guidance of Scientific Committee: Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. EFSA Journal 2011;9(5):2140 [36 pp.]. doi:10.2903/j.efsa.2011.2140 (<http://www.efsa.europa.eu/en/efsajournal/pub/2140.htm>)

In the food area, EFSA assessed the safety of silver hydrosol¹⁴³ and titanium nitride¹⁴⁴ for use as food contact materials. Titanium nitride, silicon dioxide (synthetic amorphous silica) and carbon black are authorised with specifications as food contact materials.¹⁴⁵

In the medicinal products area, EMA has been examining applications of nanotechnologies to medicinal products since 2006.¹⁴⁶ To date, recommendations from the EMA Committee for Medicinal Products for Human Use (CHMP) has led to the approval of about twenty medicines based on nanotechnology. They include medicines containing liposomes (microscopic fatty structures) containing active substances, such as doxorubicin¹⁴⁷; mifamurtide¹⁴⁸ and doxorubicin¹⁴⁹ and nanoscale particles of active substances, such as paclitaxel¹⁵⁰, aprepitant¹⁵¹ and sirolimus^{152 153}.

Marketed medical devices using nanotechnologies concern a broad range of medical applications, ranging from traditional medical equipment to sophisticated electronic biomimetic devices via orthopaedic, dental or cardiovascular implants and novel treatments against cancer. A report published by the French Health Products Agency (AFSSAPS) on 18 August 2011 lists 17 products in the EU alone.¹⁵⁴ Some national authorities in the EU Member States have developed specific guidance. The European Commission envisages addressing the issue of nanomaterials in the context of the revision of the medical device legislation planned for 2012.

In the cosmetics area, the European Commission mandated the SCCS to develop guidance on nanomaterial risk assessment, including criteria for their categorisation¹⁵⁵ and assess four

143 The assessment of silver hydrosol was inconclusive as insufficient data were provided.
144 <http://www.efsa.europa.eu/en/efsajournal/pub/888.htm>
145 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:012:0001:0089:EN:PDF>
146 EMA Reflection paper on nanotechnology-based medicinal products for human use (29/06/2006) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&mid=WC0b01ac05800baed9&jsenabled=true##).
147 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000089/human_med_000683.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
148 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000802/human_med_000899.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
149 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000297/human_med_000916.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
150 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000778/human_med_000620.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
151 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000527/human_med_000760.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
152 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000273/human_med_001010.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124
153 http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp&mid=WC0b01ac05800baed9&jsenabled=true
154 http://www.afssaps.fr/content/download/35302/460749/version/1/file/RapportNanoDM_GB_Aout2011.pdf
155 http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_q_056.pdf

nanomaterials used as UV-filters (titanium dioxide, zinc oxide, ETH-50, HAA299).¹⁵⁶ On 11 November 2011, SCCS concluded that the use of 10% ETH-50 is safe for dermal application but that sprays containing ETH-50 cannot be recommended until additional information is provided. The evaluation of the other three materials is ongoing.

Absence of product recalls

The EU has two rapid alert systems, one for products (Rapid Alert System for Non-Food Dangerous Products, RAPEX¹⁵⁷) and one for food and feed (Rapid Alert System for Food and Feed, RASFF¹⁵⁸). No nanomaterial has so far been recalled under RAPEX or RASFF.

5.2. REACH registration dossiers

In close collaboration with ECHA, the Commission has assessed how nanomaterials have been addressed in REACH registration and CLP notification dossiers. At the end of February 2012, 7 registrations and 18 notifications had ticked the voluntary field "nanomaterial" as the form of the substance¹⁵⁹. The further assessment identified three groups of registration dossiers, where a) the registrants recognized nanomaterials (8 dossiers /5 substances); b) substances exist only as nanomaterial (12/9), and c) the assessors identified nanomaterials on the basis of the particle size distribution (5/5). It is possible that additional substances with nanoform(s) may have been registered or notified but were not retrieved from the REACH and CLP database when the search-term "nano" was not used in any text field in the dossier or when the other search criteria used were not fulfilled.

In the assessed dossiers, different ways were used to present identification of substances that include or in one case exclude, nanoforms, and to organize nanoform(s) relevant information. Within groups a) and b) data could generally be linked to nanomaterial but, in particular for the a) group, its data quality was often in question due to the lack of justification or adequate characterisation of the addressed nanoform(s) or the testing material. For the group c) it was not possible to distinguish which data are for nanomaterial. These findings can partly be explained by the absence of detailed guidance to registrants on registration for nanomaterials, the absence of a definition of nanomaterial and the general wording of the REACH annexes.

5.3. The conclusions from RIPoNs on the applicability of the testing strategies to nanomaterials

The Commission's Joint Research Centre carried out a number of REACH Implementation Projects on Nanomaterials (RIP-oNs) to evaluate the applicability of the existing REACH guidance to nanomaterials, and if needed, to develop specific advice on how the guidance could be updated to better address nanomaterials. Three reports are available:

RIP-oN 1 relates to "Substance identification of nanomaterials". Under REACH, substance identification determines whether substances must be registered separately or data on the same substance must be shared between the registrants. The objective of the project was to evaluate the applicability of existing guidance and, if needed, to develop specific advice on

¹⁵⁶ http://ec.europa.eu/health/scientific_committees/consumer_safety/requests/index_en.htm

¹⁵⁷ http://ec.europa.eu/consumers/safety/rapex/index_en.htm

¹⁵⁸ http://ec.europa.eu/food/food/rapidalert/index_en.htm

¹⁵⁹ Updated figures for REACH registrations based on new submissions; for original assessment see SWP, appendix 3

how to establish the substance identity of nanomaterials. The opinions of the participating experts from Member State Competent Authorities, industry, NGOs and ECHA diverged on several key issues, including whether size or surface treatment/functionalisation should affect substance identification or characterization of physicochemical properties. It was not possible to reconcile these opinions. Therefore, the report¹⁶⁰ mainly describes options/approaches rather than providing explicit recommendations. ECHA has been asked to develop such recommendations as it starts gaining practical experience through the evaluation of relevant registration dossiers.

The objectives of the RIP-oN 2 report on "Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH"¹⁶¹ were to provide advice how REACH information requirements on intrinsic properties of nanomaterials can be fulfilled, including the appropriateness of the relevant test methods (and dosimetry) for nanomaterials, and outline, when relevant, possible specific testing strategies. It was also set to provide advice on the information that is needed for safety evaluation and risk management of nanomaterials. The objective of the RIP-oN 3 project "Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH" was to develop advice on how to do exposure assessment for nanomaterials within the REACH context and how to conduct hazard and risk characterisation for nanomaterials.

Neither RIP-oN 2 or RIP-oN 3 specifically addressed presentation of information on multiple nanoforms within dossiers (RIP-on 1 task) or the practical implications of multiple nanoforms of the same substance for chemical safety assessment. The reports however recognize the possibility, when scientifically justified, to apply the same data for different forms and substances (read across, grouping) and to use non-testing approaches (e.g. (Q)SAR, in silico). They also recommend further research on non-testing approaches as a high priority to be addressed within the short term.

RIPoN 2 concludes that the existing guidance and the information requirements on (eco)toxicological data (based on the OECD Test Guidelines and ISO/CEN standards) are considered applicable for the assessment of nanomaterials. Attention needs to be given to measuring, dosing, delivery and tracking of nanomaterials in the test system. Representative sample preparation and thorough and accurate physico-chemical characterisation using multiple techniques are an essential component of assessing the potential (eco)toxicity of nanomaterials. The report proposes the introduction of additional physico-chemical property information requirements and of an advisory note on sample preparation.

The guidance on physico-chemical properties was considered to be generally applicable to nanomaterials. However, the limited relevance and applicability of the property and methods for surface tension, flash point and viscosity was recognized, and the further evaluation of suitability of existing methods for water solubility, partition coefficient, adsorption/desorption was recommended.

The guidance on toxicological Information Requirements is considered applicable, although it was highlighted that attention needs to be given to measuring, dosing, delivery and tracking of nanomaterials in the test system. In general, the basic ecotoxicological properties and endpoints described in the OECD Test Guidelines for the determination of potential effects of test substances in relevant environmental compartments (aquatic, terrestrial, sediment) after

¹⁶⁰ http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon1.pdf

¹⁶¹ http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf

acute or chronic exposure were considered adequate and relevant for nanomaterials. However, the report acknowledges the fact that OECD Test Guidelines were not specifically designed for the testing of nanomaterials, and the guidance provided on important measurement aspects such as the sample preparation, the delivery of test substances to test system or the exposure quantifications/metrics, in all of these test guidelines is considered to be insufficient for testing of nanomaterials. These issues have been preliminarily addressed in the OECD specific Preliminary Guidance Notes on Sample Preparation and Dosimetry.¹⁶²

The identified potential additional relevant specific intrinsic properties include:

- (a) Physico-chemical properties (Particle shape, Surface area, Surface energy, Surface chemistry, Surface charge, Redox potential, Cell-free ROS/RNS production capacity, State of dispersion, State of agglomeration). Additional guidance chapters were recommended only for shape and surface area;
- (b) Toxicological endpoints (Cell uptake, Cell viability, Oxidative stress, Inflammation, Fibrosis, Immunotoxicity/sensitisation, Cardiovascular toxicity); no additional guidance chapter for them was recommended;
- (c) Ecotoxicological endpoints, Ventilation rate, Gill pathologies, Mucus secretion, Brain pathology, Animal behaviour, Oxidative stress biomarkers¹⁶³; no additional guidance chapter for them was recommended.

On certain endpoints¹⁶⁴ there was limited or no body of evidence available to inform the provision of specific practical advice. The published scientific evidence demonstrated that representative sample preparation and thorough and accurate physico-chemical characterisation using multiple techniques is an essential component of assessing the potential (eco)toxicity of nanomaterials. Factors such as the exposure method, dose selection, species used, cell type under investigation, as well as coating/functionalisation of the surface and particle impurities, release of free metal ions and particle aggregation all have the potential to impact on the assessed (eco)toxicity of nanoparticles. The full extent of influence of these factors on (eco)toxicological impact of nanomaterials is however still emerging.

While, in general, it was reported that only minor updates are necessary to some of the existing Integrated Testing Strategies (ITS) for the intrinsic properties/endpoints considered, a substantive update to the ITS for particle size analysis (or granulometry) was recommended, together with the expressed need to justify scientifically the use of QSAR and/or read-across. Advice was provided on the scientific basis for the categorisation of nanomaterials and application of *in silico* methods, read-across and category approaches for deriving hazard information for nanomaterials from the information on bulk substances or from comparison between nanomaterials. Whilst the lack of data across a wide range of structural and compositionally different nanomaterials precludes a fully prescribed category-based approach being developed, the suggested approaches for possible development indicate where such groupings may be applied.

¹⁶² OECD No. 24 - ENV/JM/MONO(2010)25: Preliminary Guidance Notes on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials.

¹⁶³ The report indicates CAT, SOD, GPX, GST biomarkers.

¹⁶⁴ E.g. dermal and respiratory sensitisation and irritation, ecotoxicological endpoints.

RIPoN 3 concludes that there is still very limited evidence to draw any generalized conclusions or recommendations for the chemical safety assessment of nanomaterials under REACH. Known exposure assessment methods are generally applicable but may still experience methodological challenges, such as how to distinguish manufactured nanoparticles from background level of natural and incidental nanoparticles. No new nano-specific risk management measures need to be developed, but it is important to include specific information on nanomaterials in the safety data sheets (SDS) and assess the effectiveness of measures in place to ensure adequate protection. Due to lack of evidence, no recommendation is provided regarding risk management measures relating to the environment or the consumer.

The exposure scenarios (ES) case studies performed under RIPoN-3 highlighted general difficulties with the application of current guidance to nanomaterials. The ‘hierarchy of control’ concept which underpins much of the Operational Conditions (OC) and Risk Management Measures (RMM) REACH guidance in this area was considered to be equally valid for nanomaterials as for other substances. There is evidence that already known control and risk management methodologies *can* provide levels of protection for workers from exposure to engineered nanomaterials. It was not considered necessary to recommend the development of new nano-specific RMMs. However, the specific protection provided against specific nanomaterials needs to be evaluated. The project found that current exposure estimation models are not validated for nanomaterials and should not be used for nanomaterials without accompanying measurement data or scientific justification.

Emissions to the workplace may be substantially reduced if a process involving engineered nanomaterials is performed in a properly designed enclosure/containment, especially when adequately addressing what happens when the containment is opened. Worker exposure can be significantly reduced or prevented through the use of correctly designed and implemented extraction ventilation and filtration. Filtration theory indicates that filtration will be effective for particles in the nanometre size range. This also applies to personal protective equipment, where several studies clearly demonstrate the potential of respirator filters to capture nanoparticles. As for chemicals in general, further work is required to evaluate human factors such as leakage around face-piece filter and test protective suits and gloves.

The RIP-oN 3 report states that at current stage, Control Banding (CB) cannot be used to demonstrate that the risks are adequately controlled, but might support users in initial selection of control measures. No guidance can be given at this time as regards preliminary medical surveillance activities, though they are likely to be beneficial in the long term. Similarly, no recommendations for risk management measures in REACH guidance relating to the environment or consumer exposure can be made at this time, due to lack of evidence.

For safety data sheets (SDS), it is important that information provided for a nanomaterial is representative, valid and provides the protection needed for the forms addressed by the SDS.

Some of the key issues in exposure estimation are the discrimination from background nanoparticles and the adequate consideration of high spatial and temporal variability. The full particle size distribution curve as well as presence of ‘bundles’ or ‘clumps’ of high aspect ratio nanomaterials should be reported when measuring, and model estimates should not be relied on alone without scientific justification and further confirmation of their validity in individual cases. Adequate particle characterisation within test systems as well as the exposure environment is important as e.g. aggregation/agglomeration of nanoparticles may affect standard toxicity tests and affect parameters such as deposition zone in the lung or uptake by organisms.

For the most part, the current guidance in relation to deriving exposure limits provides sufficient flexibility to address areas of uncertainty, data gaps and, if justified, deviations from the default approach and the current assessment factors derived from classical (soluble substance) toxicity. Regarding hazard and risk characterisation, an alternative approach for extrapolating from experimental animals to humans for inhalation exposure was suggested for consideration and development.

RIP-oNs 2 and 3 work identified the critical items on exposure/dose descriptors and outlined needs for adequate exposure assessment metrics/parameters compatible with those used for hazard assessment. The metrics currently used in risk assessment across exposure, toxicology and risk, are based on mass or number. Based on toxicological evidence on inflammation, the most prominent emerging alternative or additional metric is surface area. With no definitive conclusions on the best dose metric, there was consensus that there should be sufficient characterisation of the forms of a substance tested to allow the dose response to be expressed in the different metrics discussed - number, surface area and mass. There are other parameters as well which can act as modifiers of the toxicity, including particle size, size distribution, density, surface modification, aggregation/agglomeration state and shape, but these parameters would not generally be considered as scalable dose quantities and do not therefore appear to conform to the current use of the term “metric” under REACH.

A comprehensive synthesis of findings, implications, issues and advice was developed and integrated through the Task Reports and the Final Project Report of the RIP-oN2 and RIP-oN3. Where considered relevant, feasible and justified, specific advice for updating REACH guidance was provided. For issues which were not currently technically/scientifically mature for developing detailed guidance, the need for further research and development was indicated. It must be noted in any case that the update of REACH guidance and thus inclusion of any of the advice from the reports into the ECHA guidance is exclusively the responsibility of ECHA.

5.4. JRC Nanohub

The European Commission’s Joint Research Centre’s (JRC) NANOhub is a comprehensive, non-public IT platform designed for addressing and hosting information on nanomaterials. It is based on IUCLID, which provides an accepted basis for regulatory use of data on chemicals in the EU. With its web-based functionality it is intended to boost interconnections and to facilitate synergies for collaboration within research projects.

It has been developed on behalf of the JRC as a tool to address nano-safety and measurements of nanomaterials, supported by an international stakeholder network from academia, industry, Member States, ISO, CEN, OECD, and NGOs. The JRC NANOhub hosts, among others, data and studies from the OECD Working Party on Manufactured Nanomaterials (WPMN) sponsorship programme on the safety testing of a representative set of nanomaterials, as well as test and measurement results on materials from the JRC Repository of Representative Nanomaterials (see also Appendix 9).

The data structure builds on IUCLID chapters and on the OECD Harmonised Templates. These chapters have been expanded to add additional templates for nanomaterial-specific endpoints listed by the OECD WPMN in the Guidance Manual of the sponsorship

programme.¹⁶⁵ Once these new templates have been tested and finalised, they will be submitted to the OECD for harmonisation and possible implementation in IUCLID.

JRC NANOhub provides features to address data quality, to create reports and dossiers, and to exchange data, and it provides collaborating parties with a facilitated frame for hosting and sharing data. In this way it facilitates cooperation between international parties and research projects using the World Wide Web. JRC NANOhub consists of independent, consortium-specific installations hosted by the JRC with options to protect confidentiality but also to share results between different consortia. A listing of hosted projects can be found on www.nanohub.eu.

5.5. Organisation for Economic Co-operation and Development: Working Party on Manufactured Nanomaterials

In 2006 the OECD Working Party on Manufactured Nanomaterials (WPMN) was established, bringing together relevant Ministries and Agencies responsible for human and environmental safety, as well as representatives from other stakeholder groups.

A formal four-year programme of work was endorsed by the OECD Chemicals Committee to cover the period 2009 to 2012 which aimed at the development of a globally harmonised approach to the management of nanomaterials.

The WPMN published a booklet¹⁶⁶ in February 2011 summarising the first five years of the programme, noting in that report its work on:

- Testing specific nanomaterials for their human health and safety evaluation, while ensuring appropriate testing methods (*in vivo* & *in vitro*), in addition to promoting the development of alternative test methods to nano-toxicity testing;
- Promoting co-operation on voluntary schemes and regulatory programmes;
- Facilitating international co-operation on risk assessment strategies;
- Developing guidance on exposure measurement and exposure mitigation at the workplace, for consumers and for the environment; and;
- Promoting the environmentally sustainable use of nanotechnology through enhancing the knowledge base about life cycle aspects of manufactured nanomaterials. This should be done at their different stages of development and applications.

This work has already started to generate guidance literature for those working in this field such as 'Preliminary Guidance Notes on Sample Preparation and Dosimetry'¹⁶⁷ and a

¹⁶⁵ ENV/JM/MONO(2009)20/REV

¹⁶⁶ A full version of the document can be found at <http://www.oecd.org/dataoecd/6/25/47104296.pdf>.

¹⁶⁷ [http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono\(2010\)25&doclang=en](http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2010)25&doclang=en)

'Guidance Manual for the Testing of Manufactured Nanomaterials (First Revision)'.¹⁶⁸ A full list of relevant OECD publications can be found on the dedicated WPMN website.¹⁶⁹

The ninth meeting of the WPMN took place in December 2011 to examine progress made on the current work plan. The tenth meeting of the WPMN is scheduled for June 2012.

5.6. Strategic Approach to International Chemicals Management (SAICM)

In 2006 the International Conference on Chemicals Management (ICCM) adopted the Strategic Approach to International Chemicals Management (SAICM).¹⁷⁰ This provides a UNEP level policy framework to promote chemical safety around the world.

In May 2009 ICCM2 adopted Resolution II/4 on emerging policy issues which covered the specific issue of nanotechnologies and manufactured nanomaterials, recognising their potential benefits and potential risks to human health and the environment.

Since then work has been taken forward to build a fuller understanding of this issue. The above Resolution prompted a number of Regional workshops on the issue led by UNITAR and the OECD and also the drafting of a Report¹⁷¹ on nanomaterials within the context of SAICM which was presented to the SAICM Open Ended Working Group in November 2011. Also during this meeting work was undertaken to develop actions that could be added to the Global Plan of Action (which acts as a guidance document and working tool to support implementation) in due course. This issue will be revisited during ICCM3 which is due to take place in September 2012.

5.7. Research on nanomaterial safety

The European Commission has started funding projects specifically addressing nanosafety since the 5th EU Framework Programme for Research and Technological Development (FP5, 1998-2002), with a regular budget increase. So far, 46 nanosafety projects have been funded. They represented a total EU investment of 130 M€ (corresponding to a total projects costs of 185 M€). The framework programme calls are conceived to cover all aspects necessary for the risk assessment and risk management of nanomaterials: physico-chemical characterisations of nanomaterials, fate and behaviour in biological and environmental media, bio-nano interactions, nano-toxicity and nano-ecotoxicity, life cycle analysis of nanomaterial-embedded products (including recycling and final treatment), measurement devices, exposure, worker protection, risk assessment tools and risk management strategies.

The EU projects are requested to join forces through the NanoSafety Cluster to maximise synergies, to facilitate the formation of a consensus on nanotoxicology in Europe; to improve the coherence of nanotoxicology studies and harmonize methods; and to provide a single voice for discussions with external bodies and to provide industrial stakeholders and the general public with appropriate knowledge on the risks of nanoparticles and nanomaterials for human health and the environment.

¹⁶⁸

[http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono\(2009\)20/rev&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2009)20/rev&doclanguage=en)

¹⁶⁹ http://www.oecd.org/document/53/0,3746,en_2649_37015404_37760309_1_1_1_1,00.html

¹⁷⁰ <http://www.saicm.org/index.php?ql=h&content=home>

¹⁷¹ <http://www.saicm.org/index.php?content=meeting&mid=124&def=4&menuid=>

6. INFORMATION AND DATABASES ON THE USE OF NANOTECHNOLOGY AND NANOMATERIALS

The European Parliament has called on the Commission to compile “an inventory of the different types and uses of nanomaterials on the European market, while respecting justified commercial secrets such as recipes, and to make this inventory publicly available”.¹⁷² The Council invited the Commission to “evaluate the need for [...] the further development of a harmonized database for nanomaterials, while considering potential impacts.”¹⁷³

While the European Parliament does not specify the meaning of the term “inventory”, in particular on whether this inventory should be presented in the form of a document or database, the Council invites the Commission to evaluate the need for the further development of a harmonized database. The Commission therefore has, in addition to the information on types and uses of nanomaterials in section 3 and Appendix 2 of this document, compiled information on existing databases in section 6.1 and Appendix 8. Section 6.2 gives information on plans to set up a European Commission web platform on nanomaterial types and uses, including safety aspects.

6.1. Existing databases on, or with relevance to, nanomaterials on the market

Databases on nanomaterials on the market can in principle be structured either from the perspective of nanomaterials (and possibly cover their uses in products in more or less concrete terms) or from the perspective of products on the market containing nanomaterials. Both approaches have been used in different existing databases. There are also databases which have elements of both. In addition, the nature of databases differs largely. An overview of existing databases is contained in Appendix 8.¹⁷⁴

A database with a clear substance-structure is REACH-IT.¹⁷⁵ REACH registrations for substances are stored in the REACH-IT database. REACH is specific for substances and it is possible to indicate that the registered substance is a nanomaterial or includes nanoforms in REACH registrations (for example, there is a voluntary tick-box to identify the substance or form of a substance as a nanomaterial). There is also ECHA advice on how to enter relevant data in IUCLID. This information is retrievable from the registration database. It is however not always easy to identify which information relates to the nanoform(s) and which information to the bulk form(s) of the substances. Also, the description of uses in REACH dossiers is rather generic, and therefore it is not possible to identify concrete applications from the REACH dossiers. A screening of the REACH registration dossiers and CLP notifications was performed to identify information about substances in the nanoform. Methodology and outcome of this work is reported in Appendix 3.

An example of a mixed database is ObservatoryNano.¹⁷⁶ Although the main aim of the database is not an exhaustive inventory of nanomaterials and their uses on the market, it contains a number of factsheets, briefings and reports which give an overview of nanomaterials, as well as product areas in which those substances are used. The database has a

¹⁷² <http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P6-TA-2009-0328&language=EN>

¹⁷³ http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/envir/118646.pdf

¹⁷⁴ Based on "Development of an inventory for consumer products containing nanomaterials", http://ec.europa.eu/environment/chemicals/nanotech/pdf/study_inventory.pdf.

¹⁷⁵ <http://apps.echa.europa.eu/registered/registered-sub.aspx#phasein>

¹⁷⁶ <http://www.observatorynano.eu/project/>

relatively strong focus on new developments in terms of research and innovation, and therefore does not always distinguish between widespread commercial use of nanomaterials and applications at the pre-market stage.

Moreover, there is a series of databases focusing on products on the market containing nanomaterials. Examples for such databases include the Woodrow Wilson database (“The Project on Emerging Nanotechnologies”)¹⁷⁷, the ANEC-BEUC 2010 inventory of consumer products containing nanomaterials (ANEC-BEUC 2010)¹⁷⁸, the online database of the German Environmental NGO ‘BUND’ (Friends of the Earth Germany)¹⁷⁹, and the nanotechnology products database of Nanowerk.¹⁸⁰ Those databases are all attempts to collect as much information as possible on products containing nanomaterials at the level of individual products and brands. However, they are neither based on systematic data collection over a wide range of products, nor is it certain that the products mentioned indeed contain nanomaterials. This is because the databases are at least partly based on claims by manufacturers which may, or may not be correct. Given the multitude of applications identified in the course of the analysis of nanomaterials on the market (see Appendix 2) and the limited number of products identified (e.g. around 1300 products worldwide for the Woodrow Wilson database), it seems however likely that those databases only cover a very small fragment of products containing nanomaterials on the market.

There are also a number of voluntary one-off reporting schemes in EU Member States such as the United Kingdom, France, Denmark, Germany and Ireland, as well as in several non-EU countries.¹⁸¹ However, those schemes only received very little feedback and generally do not give a satisfactory overview of nanomaterials on the market. France has recently introduced regulatory measures for a mandatory registry for substances at nanoscale, mixtures from which nanomaterials can be released, and articles with an intended release of nanomaterials.

In addition to the product databases listed above, an overview is presented in Appendix 8 on databases not predominantly considering products, but containing information related to the potential toxicity or hazard of nanomaterials. Two of those databases provide information on experimental data and the projects and/or organisations in which these data are obtained. Two other databases specifically focus on industry needs.

- (2) The OECD Database on Research into Safety of Manufactured Nanomaterials
- (3) JRC NanoHub
- (4) nanotech-data.com
- (5) nanoproducts.de

6.2. Plans for a European Commission web platform on types and uses of nanomaterials, including safety aspects

The interest in an inventory/harmonised database expressed by the European Parliament and the Council reflects a widely perceived lack of information on nanomaterials on the market.

¹⁷⁷ <http://www.nanotechproject.org/inventories/consumer/>

¹⁷⁸ www.beuc.org

¹⁷⁹ <http://www.bund.net>

¹⁸⁰ <http://www.nanowerk.com/products/products.php>

¹⁸¹ for more information: <http://nanomaterialsconf.eu/documents/Nanos-Reporting-Mechanisms.pdf>.

Existing databases are either not clear enough on the types of uses of nanomaterials, or are rather sketchy and incomplete in terms of products containing nanomaterials. In some cases, there is little quality control of the information, and therefore there are doubts on the factual correctness of at least part of the contained information. The Commission therefore has gathered available information in Appendix 2 to this Staff Working Paper.

However, the Commission understands that there is an interest in keeping this information updated and completed by new information on nanomaterials and products containing nanomaterials. The Commission is ready to host an inventory in the form of a web platform on nanomaterials and their uses. Preparatory work to set up such a web platform, led by the Commission's Joint Research Centre, has already started. Discussions among the responsible Commission services on capturing specific requirements have been initiated in order to support the European Commission's policies such as environment, consumers, health, business, employment and innovation.

The web platform should enable the user to retrieve comprehensive information on nanomaterials, presenting that information in an easily searchable way and linking to the main information sources and databases. This web platform will both present general summary information on nanomaterials and their uses, including safety aspects, building on the present Staff Working Paper, and link up to and build upon various existing or planned activities (e.g., JRC NANOhub, OECD WPMN, French Grenelle 2 bill, and others). Depending on the intended users of such a web platform (consumers, downstream/workplace users, regulators, researchers) it is necessary to consider what kind of information should be available to these different groups, and certain filtering mechanisms should be considered. A web platform design would be advantageous which would be able to incorporate existing information and be at the same time capable of being adaptable to future options.

Strengths and weaknesses of existing databases on nanomaterials and/or products containing nanomaterials are being analyzed. Publicly available databases/inventories of nanomaterials and their use often lack clear criteria for inclusion, quality assurance of the data content and being up to date. These shortcomings should be addressed, and for the part of information handled under the responsibility of the Commission, appropriate quality assurance, sustaining and periodic updating of the information should be guaranteed.

Work towards a harmonized European web platform will benefit from the recently concluded project on "Development of an inventory for consumer products containing nanomaterials" carried out by RIVM on behalf of the Commission.¹⁸² A data model was already developed in that project to record a multitude of nanomaterial relevant information related to a product in a structured manner. Furthermore, a methodology was developed to identify consumer products on the EU market containing nanomaterials, and it was subsequently used to populate a pilot version of a searchable database containing such products.

When setting up such a harmonised Commission database it will also be necessary to take into account the situation in Member States where regulatory measures (France) or discussions were already initiated in parallel to activities within the Commission.

¹⁸² <http://ec.europa.eu/environment/chemicals/nanotech/index.htm>

Appendix 1

Types of nanomaterials

1. INTRODUCTION

This Staff Working Paper is focused on the materials that meet the EU definition of *nanomaterial* (see Chapter 2). The EU has defined this single term while being well aware of the heterogeneous range of materials it covers, as shown in Chapter 3. This appendix provides an overview of the most important and common *types* or *subcategories* of nanomaterials, based on the EU definition of nanomaterial, but using also the more extensive nanomaterial terminology developed by ISO.¹⁸³ The appendix thereby also intends to clarify the relation between the EU and ISO nanomaterial definitions.

Section 1 explains and defines a number of basic terms which are used to describe and categorize nanomaterials. Section 2 lists the types of nanomaterials which are covered by the current EU definition of the term "nanomaterial". Section 3 discusses materials which do not comply with the current EU definition, but which fall under the scope of the broader ISO definition of *nanomaterial*, and which may have to be considered in the review of the current EU definition, scheduled before end 2014.

1.1. Basic terms and definitions

Nanoscale

The key term in most of the definitions of terms used in nanotechnology and nanosciences is the term *nanoscale*. Unless otherwise specified, and in accordance with ISO and EU practice, this term has in this document been used as short for the range from 1 nm to 100 nm.¹⁸⁴

Nano-objects

ISO/TC 229 (the ISO Technical Committee on Nanotechnologies) invented the word *nano-object* and defined it (first in ISO/TS 27687:2008, later confirmed in ISO/TS 80004-1:2010) to describe particles which have at least one of their 3 (orthogonal) external dimensions in the nanoscale.¹⁸⁵ Several subclasses of nano-objects are distinguished, such as *nanoparticles* (nano-objects with all 3 external dimensions in the nanoscale), *nanofibres* (grouping *nanorods* and *nanotubes*), and *nanoplates*.¹⁸⁶ All particulate materials consisting for more than 50 % of nano-objects fall under the EU definition of nanomaterial.

Aggregates and agglomerates, primary and secondary particles

Nano-objects, like other particles, have a natural tendency to agglomerate: they form groups which are held together by weak forces (e.g., van der Waals forces) or by simple physical entanglement. The tendency to form *agglomerates* generally increases with decreasing

¹⁸³ The ISO definitions of these terms can be found in the ISO Concepts database (<http://cdb.iso.org>).

¹⁸⁴ The fact that the EU definition does not refer to "approximately" 1-100 nm will in practice play little role in this typology which is not intended to refer to individual borderline cases but rather to general patterns.

¹⁸⁵ ISO TS 80004-1:2010 Nanotechnologies – Vocabulary – Part 1: Core terms

¹⁸⁶ CEN ISO TS 27687:2009 Nanotechnologies – Terminology and definitions for nanoparticles

particle size due to the higher surface energy and because inertial forces, which can 'deconstruct' agglomerates for example during sonication, become relatively less important with decreasing volume/surface area ratio.

Often, nano-objects are encountered in the form of *aggregates*. Aggregates are groups of particles which, unlike agglomerates, are held together by strong forces (for example covalent chemical bonds) or by complex physical entanglement. Aggregates are most often created during the processing of the nano-objects, e.g., when they are formed in a hot gaseous phase and collide with each other at a temperature above or near to their melting temperature.

Both aggregates and agglomerates are also called *secondary particles*, as they consist of groups of smaller, so-called *primary particles*. It is difficult and often impossible to turn aggregates back into individual primary particles other than by high-energy processes such as mechanical milling or abrasion. On the other hand, the number of primary particles in an agglomerate can change easily, e.g., under the influence of changing environmental conditions. Correspondingly, the methods to distinguish between agglomerates and aggregates are based on the detection of the change in size of the secondary particles upon sonication or upon the change of pH or other environmental conditions.

Both agglomerates and aggregates of nano-objects are covered by the EU definition of nanomaterial.

Nanostructure

The current ISO definition for nanostructure is 'a composition of inter-related constituent parts, in which one or more of those parts is a nanoscale region, where a region is defined by a boundary representing a discontinuity in properties'¹⁸⁷ Examples of a nanoscale region are nanophases or nanopores.

Dispersion

A dispersion is a material that consists of a dispersing medium (a continuous, matrix phase) and a dispersed phase (a collection of particles or small phases of the same kind, which are separated from each other by the dispersing medium). Both the dispersing medium and the dispersed phase can be solid, liquid or gaseous, leading to a number of possible combinations:

	Dispersed phase		
Continuous phase	solid	liquid	gas
solid	(kind of) composite material	porous material filled with liquid	porous material filled with gas
liquid	suspension	emulsion	foam
gas	aerosol	aerosol	(does not apply)

¹⁸⁷ ISO TS 80004-1:2010 Nanotechnologies – Vocabulary – Part 1: Core terms

1.2. Nanomaterials – general definitions

The EU definition of nanomaterial

The EU definition of nanomaterial has been shown in Chapter 2 of this Staff Working Paper, which explains how the definition was developed and on which materials it is focused. In the Recommendation on the nanomaterial definition, the Commission commits to review its current definition by December 2014, in the light of experience and of scientific and technological developments. In particular, the review should assess whether the number size distribution threshold of 50 % should be increased or decreased and whether to include materials with internal structure or surface structure in the nanoscale such as nanoporous and nano-composite materials. For this reason, it is useful to look also at the current ISO definition, which is broader and inter alia includes nanostructured materials other than aggregates and agglomerates.

The International Organization for Standardization (ISO) definition of nanomaterial

Section 1.1 lists a number of terms and concepts used to describe features of materials that are called nanomaterials. ISO has used these terms in its definition of the term nanomaterial in its Technical Specification 80004-1¹⁸⁸:

“A nanomaterial is a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale

Note 1: This generic term is inclusive of nano-object and nanostructured material.

Note 2: See also engineered nanomaterial, manufactured nanomaterial and incidental nanomaterial.”

As is the case for all ISO Technical Specifications, this definition will have to be confirmed in a full ISO standard, or be revised.¹⁸⁹ Some of the questions to be solved are:

- is one single nano-object a *nanomaterial*?
- since all materials have a structure at the nanoscale, is everything a nanomaterial?

The first question is implicitly answered in the EU definition, which considers nanomaterials to be particulate materials with a particle size distribution. Single nano-objects do not have a particle size distribution, and have no industrial or market relevance. It is expected that ISO will consider, inspired also by the EU definition, an additional term such as particulate nanomaterial to cover 'materials consisting of nano-objects'.

The second question is one of the reasons why nanostructured materials are not covered by the current EU definition. ISO has considered the issue of nanostructured materials in the recently released ISO TS 80004-4 (Nanotechnologies – Vocabulary – Part 4: Nanostructured

¹⁸⁸ ISO TS 80004-1:2010 Nanotechnologies – Vocabulary – Part 1: Core terms.

¹⁸⁹ ISO Technical specifications shall be reviewed at least every three years to decide either to confirm the technical specification for a further three years, revise the technical specification, process it further to become an International Standard or withdraw the technical specification. After six years, a technical specification shall be either converted into an International Standard or withdrawn.

Materials)¹⁹⁰, which limits the nanoscale features that can turn a material into a nanomaterial, in the following way:

"A material should not be classified as nanostructured based solely on its crystalline properties (three-dimensional arrangements of atoms or molecules forming a crystallite, short range order of atoms in amorphous or quasi-amorphous phases, grain boundaries, intragranular interfaces, dislocations, etc.). In contrast, materials with a grain size distribution having a significant fraction of grains in the nanoscale (nanocrystalline), voids and pores in the nanoscale, or precipitations in the nanoscale (i.e., nano-objects in a solid matrix) are sufficient features for materials to be classified as "nanostructured" (see ISO/TS 80004-1, 2.4 nanomaterial). Similarly, almost all materials always have surfaces with morphological and chemical heterogeneities in the nanoscale. Only surfaces that have been intentionally modified or textured to have morphological or chemical heterogeneities in the nanoscale identify materials as "nanostructured"."

2. TYPES OF NANOMATERIALS MATCHING THE EU DEFINITION

A number of materials meet both the current EU and ISO nanomaterial definitions. Basically, these are the particulate nanomaterials, which consist of nano-objects or contain a major fraction thereof.

2.1. Nanostructured powders and nanopowders

A powder is an assembly of discrete particles usually less than 1 mm in size.¹⁹¹ According to ISO/TS 80004-4 a nanostructured powder is a powder comprising nanostructured agglomerates, or nanostructured aggregates, or other particles of nanostructured material. In this definition, the nanostructured aggregates and agglomerates are collections of individual nano-objects, and therefore they match the EU definition.

It must be noted that no term has yet been assigned to powders consisting of non-aggregated and non-agglomerated nano-objects. ISO has the intention to close this gap, possibly using the term nanopowder. Conceptually even simpler than nanostructured powders, nanopowders seem to be the most straightforward kind of nanomaterials, matching also the EU definition. However, the term is of limited practical relevance given the strong tendency of nano-objects to agglomerate. To avoid the agglomeration of nano-objects, they need to be dispersed in liquid (see section 2.2).

The family of nanostructured powders and nanopowders can be subdivided based on the shape of the included nano-objects (equiaxial: nanoparticles; elongated: nanofibres, nanotubes or nanorods; flat: nanoplates). Alternatively, subdivisions can be made based on the element or compound of which the nano-objects consist. It is possible, at least in theory, to produce nanostructured powders of almost all elements or compounds which at ambient conditions are in the solid state (metals, polymers, ceramics).

¹⁹⁰ ISO TS 80004-4:2011 Nanotechnologies – Vocabulary – Part 4: Nanostructured Materials.

¹⁹¹ ISO 3252:1999 Powder metallurgy – Vocabulary.

2.2. Nanosuspensions

A nanosuspension consists of solid nano-objects suspended or dispersed in a liquid phase. A common term to denote a similar class of materials is the term 'colloid'. (Note: The upper size limit of the particles in a colloid system varies in different definitions of the term between 100 nm¹⁹² and 1000 nm.¹⁹³)

2.3. Nano-aerosols

Nano-aerosols are materials which consist of a gaseous phase containing freely moving nano-objects. It is not straightforward to produce nano-aerosols with sufficient stability to allow trade and transport. Rather, these materials are produced, intentionally or unintentionally, at a certain place and time. Both intentionally and unintentionally produced nano-aerosols are relevant from a regulatory point-of-view, and are included in the EU definition of nanomaterial, if the dispersed particles are solid.

3. TYPES OF NANOMATERIALS NOT MATCHING THE EU DEFINITION

A number of materials meet the ISO (or other) nanomaterial definition(s), but not the EU definition. Basically, these are nanostructured materials and materials containing liquid or gaseous 'particles'. The more common kinds of these materials are listed below.

3.1. Nano-emulsions

Nano-emulsions consist of liquid nano-objects suspended or dispersed in a liquid phase. They are not covered by the EU nanomaterial definition, because the term particle as defined in the Commission Recommendation is intended to cover only nano-objects with a defined, rigid shape¹⁹⁴, thus in essence solid nano-objects.

3.2. Particles with an engineered nanoscale internal structure (if larger than 100nm)

Nano-objects are particles with at least one external dimension at the nanoscale. There are an increasing number of particles which are engineered to have internal nanoscale features. Examples are *core-shell particles* and *nano-encapsulates*. These particles may be designed, for example for pharmaceutical applications, where the inner core particle is "released" in a certain environment. Some of these materials have an external diameter smaller than 100 nm, matching the EU nanomaterial definition, others have an external diameter larger than 100 nm, not matching the EU nanomaterial definition. In ISO terms also the latter qualify as nanomaterials, based on the nanoscale thickness of their shell or capsule or based on the nanoscale diameter of the core particle.

3.3. Nanocomposite materials

Nanocomposite materials (or nanocomposites) consist of at least two different phases, at least one of which has nanoscale features. Well-known examples are matrix materials reinforced with carbon nanotubes (e.g., polymer matrix composites with finely dispersed nanotubes for improved electrical conductivity).

¹⁹² ISO 1942-2-:1989, Dental vocabulary – Part 2: Dental materials.

¹⁹³ R.J. Hunter, Foundations of Colloid Science, Oxford University Press, 2001.

¹⁹⁴ http://ec.europa.eu/environment/chemicals/nanotech/questions_answers.htm, question 3.

There is a debate about the need to include more 'traditional' materials under this definition, such as steels or other metals, which often have a carefully designed microstructure with nanoscale elements such as precipitates, which improve for example the mechanical properties of the material.

3.4. Nanoporous materials and nanofoams

Nanoporous materials

Nanoporous materials are materials containing a fraction of small, nanoscale pores. The defining property here is the size of the nanopore. As such, they are not covered by the nanomaterial definition (e.g. zeolites). However, when the nanoporous materials consist of aggregates/agglomerates of particles in nano-size (see Chapter 2.1), they fall under the EU definition (e.g. silica gels).

Liquid nanofoams

A liquid nanofoam consists of nanoscale gas bubbles surrounded by liquid struts. They are not covered by the EU nanomaterial definition, because the term particle as defined in the Commission Recommendation is intended to cover only nano-objects with a defined, rigid shape¹⁹⁵, thus excluding gas bubbles.

Solid nanofoam and nanoporous material

A solid nanofoam consists of nanoscale gas bubbles surrounded by solid struts. The defining property can be either the size of the nanopores or the scale of the strut material. Also, the material can contain two continuous phases, if the pore volumes are interconnected, in which case it is the cross-section or thickness of the solid struts that has to be in the nanoscale.

A nanoporous material is a solid material containing nanopores. The term is overlapping with the term nanofoam, but the fraction of pores in the nanoporous materials is more limited than in a nanofoam.

¹⁹⁵ http://ec.europa.eu/environment/chemicals/nanotech/questions_answers.htm, question 3.

Appendix 2 Nanomaterials on the EU market

1. INTRODUCTORY REMARKS AND INFORMATION SOURCES

This appendix is intended to give an overview of the nanomaterials on the market as well as their uses. Its focus is on giving an overall picture of the market, rather than being exhaustive or concrete in specific applications.

Most of the information is taken from SRI Consulting reports.¹⁹⁶ Those reports are explicitly referenced to where they concern numbers or estimates but not where they concern general information. The general information on nanomaterials on the market and their applications is normally also from those reports if not otherwise quoted. In addition and on specific subjects not covered by those reports, the chemistry and materials sectoral reports of ObservatoryNano¹⁹⁷, the DaNa Knowledge Base Nanomaterials¹⁹⁸ or other public sources were used. Where available, information is included on coverage of nanomaterials in REACH dossiers and classification and labelling by registrants. This information was taken from the ECHA website¹⁹⁹ and the ECHA analysis on “Information on Nanomaterials retrieved in the ECHA Databases for REACH Registrations and CLP Notifications” (see Appendix 3) as well as joint work between ECHA and the Commission services analysing a number of registration dossiers in more detail. The classification information is mostly (though not always) unspecific and it is difficult to deduce whether the information provided relates to the bulk or nanoform(s) of the substance. Information on the reasons for (non)classification (e.g. data lacking, conclusive but not sufficient for classification, etc.) is given in footnotes. Moreover, this appendix takes into account contributions received as a result of a consultation of the members of the REACH and CLP Competent Authorities Subgroup on Nanomaterials (CASG(Nano), including representatives from Member States, industry and non-governmental organisations)²⁰⁰ on a draft of this appendix. Safety information is taken mainly from the ENRHES report²⁰¹, EU-OSHA and the DaNa Knowledge Base Nanomaterials.²⁰²

In principle, this appendix follows the definition of nanomaterial as laid down in Commission Recommendation 2011/696/EU. However, in most cases the same substance exists in particle sizes below and above 100 nm, and it is sometimes unclear whether the collected information refers to one or the other, or both. Normally, this is indicated in the relevant sections. This

¹⁹⁶ Source: IHS Inc. The use of this content was authorized in advance by IHS. Any further use or redistribution of this content is strictly prohibited without written permission by IHS. All rights reserved. Reports used: Stefan Schlag, Bala Suresh, Masahiro Yoneyama and Vivien Yang, <http://www.sriconsulting.com/SCUP/Public/Reports/NANOT000/>; references to SRI in this annex refer to this report, except for carbon black, where information was taken from the Chemical Economic Handbook report on carbon black <http://www.sriconsulting.com/CEH/Public/Reports/731.3000/>.

¹⁹⁷ <http://www.observatorynano.eu/project/catalogue/2CH/>

¹⁹⁸ <http://www.nanopartikel.info/cms/lang/en/Projekte/dana>; note that the database in many cases refers to “high dose” experiments. Such “high dose”-experiments describe situations which do usually not occur in normal life, neither for a customer nor at an industry’s workplace. High dose exposures could occur in case of an accident or a wanted uptake of nanoobjects.

¹⁹⁹ <http://apps.echa.europa.eu/registered/registered-sub.aspx#phasein>

²⁰⁰ Document CASG Nano/03/2011.

²⁰¹ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>.

²⁰² <http://www.nanopartikel.info/cms/lang/en/Wissensbasis>

appendix is in principle structured according to chemical substances which are nanomaterials or have forms which are nanomaterials.²⁰³ This follows in essence the REACH substance definition, without prejudice to whether the substance only exists as nanoform or whether the substance has different bulk and nanoforms. The presented information may either refer to the substance as such or to specific nanoforms, or, in certain cases to groups of substances (e.g. polymers) or even broader material categories (e.g. quantum dots). This is done because it would not be possible to strictly distinguish all relevant information according to substance or form. Therefore, this listing is a pragmatic way to present information in the most structured way possible but not a scientific categorisation. While aiming at a structured approach in describing the different nanomaterials addressing the relevant features, the level and detail of presented information varies significantly. This is because of strong differences in the quality and detail of information that could be found. If information that is given for some nanomaterials is missing for others, this normally means that relevant information could not be identified or was of a quality which was considered insufficient for presentation in this context. In the context of REACH registrations, the absence of information normally means that no relevant registration could be identified.

Where appropriate, clarification as to whether information relates to bulk or nanoforms is provided but often this is not possible and the information is presented as relating to the “substance” (in particular in the context of REACH registrations). There are also variations of the substances, reaction masses²⁰⁴ etc. which have been registered in addition to the below list but which are not detailed here because there is insufficient information to link them clearly to available market information.

In general, the below information is focused on applications already on the market (including medical applications). Applications at the stage of research and development (R&D) are normally not specifically mentioned, although it cannot be excluded that some of the information relates to products at R&D stage. There are also new types of nanomaterials in development, which are often referred to as “second generation” (targeted drug delivery systems, adaptive structures and actuators), “third generation” (novel robotic devices, three-dimensional networks and guided assemblies), and “fourth generation” (molecule-by-molecule design and self-assembly capabilities) nanomaterials.^{205,206,207} However, those are either at research or development stage or at an early stage of market development. Due to the limited available information on those materials, they are not further considered in this Staff Working Paper.

Military applications are normally not mentioned. In most applications, the nanomaterial is present in the final product, either as aggregates or agglomerates (rarely, if at all, as free particles) in a mobile form or bound in a matrix or included in closed applications. There

²⁰³ In terminology developed in the framework of REACH implementation “substances at the nanoscale”; for discussion of this terminology, see http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/nanomaterials_en.pdf. Normally, substances are described in their chemical identity, as defined in REACH.

²⁰⁴ For an explanation of the term “reaction mass”, see REACH guidance on substance identification and naming http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.pdf, p. 21.

²⁰⁵ Roco, M. C. 2004. Nanoscale Science and Engineering: Unifying and Transforming Tools. *AIChE Journal*, 50(5): 890-897.

²⁰⁶ Roco, M. C. 2007. National Nanotechnology Initiative– Past, Present, Future.” In Goddard, W. A., et al. eds. *Handbook on Nanoscience, Engineering and Technology*, Boca Raton, FL, CRC Press; pp. 3.1-3.26.

²⁰⁷ <http://www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf>, p. 12.

may, however, also be cases where the nanomaterial is only used as an ingredient for the production of the mentioned applications, during which the nano-ingredient loses its particulate character (through dissolution) or its nanoscale character (through particle growth or fusion).

This appendix aims to give a good and structured overview of nanomaterials on the market. It can, however, not give a complete or exhaustive list of nanomaterial forms or variations which are often tailored in a very specific way to achieve desired properties, and which may also to a certain degree have different toxicological and ecotoxicological properties. Depending on the concrete cases, these differences may be smaller or larger. Therefore, wherever in this appendix reference is made to the nanoform, this is often not one singular form but refers to variations in particle size, shape, surface treatment, functionalisation etc.

In preparing this appendix, the European Commission also aimed at identifying information on the relevant competitive position of EU companies and production sites, as well as on market volumes for the EU. However, in general it appears that most substances are produced all through the industrialised world, with producers in Europe, North America (mainly United States and Canada) and Japan or other traditionally industrialised countries in the Far East. Often there are also producers in newly industrialised countries such as China, India, Russia or Brazil. However, data on producers are not complete, both for the industrialised countries and even more so for emerging countries. Therefore, it does not seem possible to give a robust picture of EU companies and production sites per substance. Rather, the broad impression is that most of the mentioned substances are produced in the EU at a comparable²⁰⁸ level to other industrialized regions, and only for few of those substances there seems to be a concentration in a particular world region. For this reason, and due to a lack of specific data for the European Union or Europe as a whole, reference is made mainly to global data. Equally, most applications of nanomaterials seem to be marketed throughout the industrialized world. Therefore, it is difficult to assess whether a particular application is available on the EU market as opposed to other geographic regions. However, for most of the applications mentioned below, there is no reason to assume that they are not present in the EU market.

All quoted production volumes are annual production volumes, unless specified otherwise. Monetary figures are mostly converted from US\$ to € at an exchange rate of 0.785, with appropriate rounding.

2. INORGANIC NON-METALLIC NANOMATERIALS

2.1. Synthetic amorphous silica (silicon dioxide, SiO₂, EC Number 231-545-4)

There are various forms of synthetic amorphous silica placed on the market, including precipitated silica, silica gels, colloidal silica or silica sols and fumed or pyrogenic silica. Most forms are either used as stable dispersions of non-agglomerated SiO₂ particles (colloidal silica) or as agglomerated or aggregated particles (other forms of silica).

²⁰⁸ The term “comparable” is to be understood as leaving a degree of uncertainty on the exact levels, thus it could not be excluded that Europe is slightly weaker in relative terms of nanomaterial uptake than e.g. the US or Japan.

Synthetic amorphous silica has been in use since the 1920ies. According to SRI, the global consumption of all types of synthetic amorphous silica was around 1.5 million tons in 2010, with a market value of around 2.7 bn€.

Colloidal silicas are stabilised dispersions of non-agglomerated, mostly spherical SiO₂ particles. The main uses are in paper industry (e.g. providing anti-slip properties; retention aids and in coatings of ink jet paper; better handling of recycled paper); chemical-mechanical planarisation (CMP) slurries (e.g. polishing agent for Si wafers used to produce computer chips); coatings, paints, inks and adhesives (increasing strength, scratch and abrasion resistance); precision metal casting and refractory (e.g. moulds for casting around wax originals); food industry (e.g. as an aid for clarifying wine, beer, fruit juices etc.); bulk plastics and composites; photography; metal surface treatment; catalysis; textile; leather; and building industry (e.g. thermal and acoustic insulation).

Precipitated silica is made up of primary particles in the size range of around 5-100 nm²⁰⁹ which are aggregated and agglomerated in the final product. The biggest use of precipitated silica is for the reinforcement of elastomer products, primarily automotive tyres, footwear, rubber articles and cable sheathing. In tyres, formulations using precipitated silica reduce rolling resistance, improve traction under slippery conditions and improve fuel efficiency. Precipitated silica is also used in batteries; as antiblocking agent in thermoplastic films; as carrier silica for liquids and semi-liquids and anti-caking agent in food powders, in health care products such as toothpastes, detergents and cosmetics; as matting agents in paints and varnishes; in the paper industry as advanced fillers in newsprint paper and in special coated papers for inkjet and direct thermal printing to enhance ink absorption; and in agricultural products.

Synthetic silica gels are products of the polymerisation process of fine colloidal silica. They have a similar structure as precipitated silica, the difference being that the cross-linked silica particle networks form a nanopore structure that is finer than the pore structure of the aggregated particles in precipitated silica. Silica gels are sold in various types of gels (hydrogel, aerogel, xerogel, etc.). They are used in many food and health products (e.g. to selectively remove certain proteins and polyphenols that precipitate upon chilling). They are used in food industry as an anticaking agent and as a carrier for vitamins and as a tableting aid in pharmaceuticals. They are also used in cosmetics such as face powders, as flow conditioner and for oil absorption. Silica gels also serve as drying agents, protecting a wide variety of products during shipment and storage. They are also used in paints, catalysts, paper coatings etc.

Pyrogenic (fumed) silica is manufactured by using the high temperature hydrolysis process developed in the beginning of the 1940s. It consists of agglomerated and aggregated primary particles. The latter are of size typically between 5 and 100 nm. The aggregates, which are fused and chemically bonded primary particles, typically are of size between 100 nm and 350 nm. The aggregates in turn form agglomerates typically in the range from 150 nm up to the several 100 µm.²¹⁰ Pyrogenic or fumed silica²¹¹ is used in silicone rubber applications, as a reinforcement and thixotropic agent in plastics, gel coats, sealants and adhesives, cosmetics and toothpastes; in coatings and printing inks; as a free flow, antistatic agent in animal

²⁰⁹ This can be different depending on process details.

²¹⁰ CEFIC, contribution received as part of the consultation on a draft version.

²¹¹ To be distinguished from "silica fume" which is a by-product from thermal silicon production processes, CEFIC, contribution received as part of the consultation on a draft version.

feedstuffs and hygroscopic powders; and carrier for active ingredients. It is also used as an antifoaming agent in the manufacture of paper, decaffeinated coffee and tea, poultry and seafood processing, and oil refining.

The substance silicon dioxide (synthetic amorphous silica) has been registered under REACH.²¹² Given the explanations in the registration dossier, referring to amorphous silica, fumed and precipitated silica, it seems however clear that the dossier mostly, if not exclusively relates to the nanoform. It has not been classified as hazardous by the registrant.²¹³

Animal data show that synthetic amorphous silica, at very high doses, can induce (mostly reversible) inflammation, cytotoxicity and tissue damage in the lungs.²¹⁴ However, treatment with lower doses is observed not to effect toxicity in animals.²¹⁵ ECETOC has made a critical evaluation of the physico-chemical properties, toxicology, ecotoxicology and environmental fate and impact of (non-crystalline) synthetic amorphous silica.²¹⁶

In its opinion of 5 June 2009, the EFSA Panel on Food Additives and Nutrient Sources concluded that the use of silicon dioxide up to 1500 mg SiO₂/day and of silicic acid gel to supply up to 200 mg silicon/day, added to food supplements, is of no safety concern.²¹⁷

Synthetic amorphous silica (primary particles in the size range 1-100 nm) needs to be distinguished from respirable crystalline silica (primary particles mostly above 100 nm). Contrary to synthetic amorphous silica, crystalline silica is known to produce silicosis, a serious chronic lung disease observed in particular with workers who have inhaled particles of crystalline silica.²¹⁸

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use/consumption and waste stages varies according to application. Exposure to humans can be significant when the amorphous silica is ingested

²¹² Synonymous for synthetic amorphous silica; public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-76fd35e0-69c4-29a3-e044-00144f26965e/DISS-76fd35e0-69c4-29a3-e044-00144f26965e_DISS-76fd35e0-69c4-29a3-e044-00144f26965e.html.

²¹³ Except for respiratory sensitisation and hazardous to the ozone layer (data lacking), all fields for health and environmental hazards indicate that the registrant considers data for those hazards as conclusive but not sufficient for classification.

²¹⁴ EU-OSHA, Workplace exposure to nanoparticles, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view

²¹⁵ For an overview of relevant literature see: http://nanopartikel.info/cms/lang/en/Wissensbasis/siliciumdioxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=384&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/siliciumdioxid/element2Category2ContainerList/ContentContainer_384; see also: Presence and risks of nanosilica in food products, Dekkers, S.; Krystek, P.; Peters, R.B.J.; Lankveld, D.P.K.; Bokkers, B.G.H.; van Hoeven-Arentzen, P.H.; Bouwmeester, H. and Oomen A.G.; Nanotoxicology, 2010, Early Online, 1-13, and comments in a letter to the editor in: Nanotoxicology, 2011; Early Online, 1–3.

²¹⁶ http://www.ecetoc.org/index.php?mact=MCSOap,cntnt01,details,0&cntnt01by_category=3&cntnt01order_by=Reference%20Desc&cntnt01template=display_list_v2&cntnt01display_template=display_details_v2&cntnt01document_id=122&cntnt01returnid=91

²¹⁷ <http://www.efsa.europa.eu/en/efsajournal/doc/1132.pdf>

²¹⁸ European schedule of occupational diseases (notified under document number C(2003) 3297).

from food, or in cosmetics and pharmaceutical applications. An important source of environmental exposure is wear of tyres.²¹⁹

2.2. Substances similar to synthetic amorphous silica

There are several substances which are similar in characteristics and applications to synthetic amorphous silica. Although they have not been widely discussed under the aspect of nanomaterials, and hence information is scarce about applications of possible nanoforms of these substances, they are likely to be at least partly nanomaterials in the sense of the nanomaterial definition. Many of those are also produced in high volumes. Examples are salts of silicic acid (e.g. silicic acid, calcium salt and silicic acid, aluminium sodium salt, other amorphous silica products), silica fume (by-product of thermal silicon production), fused silica and polymerised forms of biogenic silica (e.g. from diatomae).²²⁰

2.3. Titanium dioxide (TiO₂, EC Number 236-675-5)

Titanium dioxide powder exists both in bulk²²¹ and nanoform, as well as in various crystalline modifications, including rutile and anatase. In its bulk form, it has been used extensively for about 90 years as the principal white pigment (maximum reflectivity at around a particle size of 300 nanometres). Titanium dioxide is also an effective UV filter. The nanoform (around 50 nanometres) is transparent, which provides an esthetic advantage for uses in sunscreens (mostly rutile). Nanoform TiO₂ in the anatase modification also has specific electrical and photocatalytic as well as antimicrobial properties. The nanoform of anatase is reported to be more reactive than the bulk form.

The substance titanium dioxide has been registered under REACH.²²² According to industry, the registration covers all forms of titanium dioxide including the bulk and the nanoform but with no specific differentiation. The substance has not been classified as hazardous by the registrant.²²³

Results from experimental animal studies show inflammogenic, oxidative and genotoxic pulmonary responses at high doses. Chronic exposure also has the potential to promote tumour development.^{224,225} There is also one study showing genotoxic responses after oral administration in animal studies.²²⁶

²¹⁹ As part of the rubber matrix.

²²⁰ Information from contributions to the CASG(Nano) consultation and joint work between ECHA and the Commission services analysing a number of registration dossiers in more detail.

²²¹ For an explanation of the use of the term “bulk”, see Nanomaterials in REACH, p.5, http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/nanomaterials_en.pdf.

²²² Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eaff323-014a-482f-e044-00144f67d031/DISS-9eaff323-014a-482f-e044-00144f67d031_DISS-9eaff323-014a-482f-e044-00144f67d031.html.

²²³ Except for hazardous to the ozone layer (data lacking), all fields indicate that the registrant considers data for all endpoints as conclusive but not sufficient for classification.

²²⁴ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 141.

²²⁵ <http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf>

²²⁶ Titanium Dioxide Nanoparticles Induce DNA Damage and Genetic Instability In vivo in Mice, Trouiller, B., Reliene, R., Westbrook, A., Solaimani, P., Schiestl, R.H., Cancer Res November 15, 2009 69; 8784. Available at <http://cancerres.aacrjournals.org/content/69/22/8784.full>.

Titanium dioxide has been in 2006 classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2B carcinogen "possibly carcinogen to humans."²²⁷ US NIOSH recommended a lower exposure limit for ultrafine particles of titanium dioxide²²⁸: 0.3 mg/m³ for TiO₂ nanoparticles (<100 nm), versus 2.4 mg/m³ for fine particles (>100nm), based on the particle surface reactivity. Although it is established that TiO₂ does not pass undamaged skin, there is an ongoing scientific debate on whether and to what degree TiO₂ nanoparticles can penetrate damaged skin. The approval for use of TiO₂ as a UV filter in sunscreens is currently being updated by SCCS.

According to SRI, the global market for nanoform TiO₂ is estimated to be about 10 thousand tonnes per year. The Commission has also received estimates which are higher than this but still in the same rough order of magnitude. Around 5 thousand tonnes per year are used in the personal care industry, of which around 430 tonnes in sunscreens. Next to sunscreens, the UV filtering properties are also used in coatings for plastics and metals, varnishes for wood preservation, in textile fibres and in packaging films. Another main use is catalysts (e.g. decomposing NO_x into nitrates or N₂). The photocatalytic and antimicrobial properties are used in 'self-cleaning' products (e.g. windows, cement, tiles, textiles for use in hospitals) and air purification systems. Use in tribological coatings prevent deposits in engines and enhance fuel efficiency. TiO₂ nanoparticles are also used to increase scratch-resistance of coatings and in the production of electronic components and dental impressions. TiO₂ can also be used in dye-sensitized solar cells to produce electricity, though efficiency is currently lower than traditional silicon solar cells.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage varies according to application. It can be high, in particular in cosmetics applications. In other applications where the nanoparticles are embedded in a matrix or used in closed systems, it is estimated to be low, especially if referring to short-term exposure. There are ongoing discussions whether leaching (e.g. of outdoor paints or release at the waste stage) could lead to exposure to significant amounts of nanoparticles.²²⁹

2.4. Zinc oxide (ZnO, EC Number 215-222-5)

Like titanium dioxide, zinc oxide powder exists in bulk and in nanoform. Its nanoform is colourless and an effective UV-filter with a different spectrum than titanium dioxide. It also has antimicrobial properties (though less strong than TiO₂) and can be used as an active agent in self-cleaning products.

²²⁷ Titanium dioxide has been in 2006 classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2B carcinogen "possibly carcinogen to humans"; <http://monographs.iarc.fr/ENG/Monographs/PDFs/93-titaniumdioxide.pdf>.

²²⁸ Occupational Exposure to Titanium Dioxide, Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide, National Institute for Occupational Safety and Health 2011. Available at <http://www.cdc.gov/niosh/docs/2011-160/>; further literature see also: http://nanopartikel.info/cms/lang/en/Wissensbasis/Titandioxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=46&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Titandioxid/element2Category2ContainerList/ContentContainer_46.

²²⁹ For further information see: http://nanopartikel.info/cms/lang/en/Wissensbasis/Titandioxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=46&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Titandioxid/element2Category2ContainerList/ContentContainer_46, section on environmental exposure.

The substance zinc oxide has been registered under REACH.²³⁰ However, the registration is unspecific to the nanoform (although certain references could be interpreted as referring to the nanoform). It has been classified as hazardous (Aquatic Chronic 1) with the following Hazard Statement (GHS): H410: Very toxic to aquatic life with long lasting effects.²³¹

SCCS currently assesses ZnO UV filters.

Like the bulk form of ZnO, ZnO nanoparticles show a relatively high toxicity for cells of different tissues and different organisms in in-vitro studies. For most cell types, the relevant value is in the range of 10-20 µg/ml. There are limited in-vivo studies on ZnO nanoparticles indicating severe but temporary pulmonary inflammatory responses. The effects for nanoscale and fine particles seem to be very similar. Zinc oxide fine particles (e.g. from zinc oxide fume, e.g. in welding) can cause metal fume fever.^{232,233}

According to SRI, the global market for nanoform zinc oxide is several thousand tonnes per year. Major uses are as a UV-filter in cosmetics (where it competes with bulk zinc oxide but has the advantage of being transparent), in varnishes (as a UV-filter and self-cleaning agent), ceramics and electronics. Nanoform zinc oxide is also used in rubber, improving toughness, increasing abrasion resistance (e.g. reducing wear loss in tyres) and preventing UV and bacterial degradation. In this way, the life time of rubber products can be prolonged. An emerging use is zinc oxide nanowires for UV nanolasers. Uses are also reported in liquid crystal displays and solar cells.²³⁴

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage varies according to application but can be high in particular in cosmetics. Another source of environmental exposure is wear of tyres²³⁵. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

2.5. Aluminium oxide (Al₂O₃, EC Number 215-691-6)

Aluminum oxide nanoparticles are widely used as fillers in polymers and tyres and to increase scratch- and abrasion-resistance in coatings.

²³⁰ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb185b3-df52-333c-e044-00144f67d031/AGGR-fbd39734-7544-4e5a-8f87-2e1d877da115_DISS-9eb185b3-df52-333c-e044-00144f67d031.html.

²³¹ Except for the classification as Aquatic Chronic 1H410: Very toxic to aquatic life with long lasting effects, and for hazardous to the aquatic environment (acute/short-term) (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²³² Zinc oxide, Registry of Toxic Effects of Chemical Substances RTECS #: ZH4810000, <http://www.cdc.gov/niosh-rtecs/ZH496510.html#P>; NIOSH Pocket Guide to Chemical Hazards, <http://www.cdc.gov/niosh/npg/npgd0675.html>.

²³³ http://nanopartikel.info/cms/lang/en/Wissensbasis/Zinkoxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=528&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Zinkoxid/element2Category2ContainerList/ContentContainer_528

²³⁴ Observatory Nano – <http://www.observatorynano.eu/project/document/79/>.

²³⁵ As part of the rubber matrix.

The substance aluminium oxide has been registered under REACH²³⁶. However, the registration is unspecific to the nanoform (although certain references could be interpreted as referring to the nanoform). It has not been classified as hazardous.²³⁷

Aluminium oxide nanoparticles show a low level of toxicity, although pulmonary inflammatory responses can be observed at very high doses.²³⁸

According to SRI, the global market for nanoform alumina powders is estimated at 200 thousand tonnes, representing a market value of €750 million. Nanoform Al₂O₃ powders and dispersions are used inter alia in scratch- and abrasion resistant coatings (e.g. for cutting and grinding tools, automobile exteriors, safety glasses and scratch-resistant windows for barcode scanners, flooring), as abrasive particles in slurries for polishing semiconductor and precision optical components, in the coating of light bulbs and fluorescent tubes, as a flame retardant, as fillers for polymers and tyres, in coatings of high-quality inkjet papers, in catalysts including the support structure in automobile catalytic converters, in refractory materials and as ceramic filtration membranes. Nanoform alumina can also be used for the manufacture of transparent ceramic bodies for high-pressure lamps.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage is estimated to be rather low as the aluminium oxide is mostly embedded in a matrix and most applications do not seem to imply an intended release. However, there could be some exposure e.g. through wear of tools or tyres. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

2.6. Aluminium hydroxides and aluminium oxo-hydroxides

There are also different aluminium hydroxide (e.g. bayerite and gibbsite) and aluminium oxo-hydroxide (e.g. boehmite and diaspore) particles in nanoform. Aluminum hydroxide Al(OH)₃ in powder form is used as a flame retardant and as filler in carpets, rubbers, plastics, and foamed plastics. Moreover, it is used in toothpaste and cosmetics. Aluminum (hydr)oxides are often used in the dye and plastics industries as thickeners and fillers and as agents that reduce adhesiveness and increase scratch resistance. Besides, they serve to enhance the color saturation of paints and varnishes.²³⁹

²³⁶ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb4460f-9f3a-575c-e044-00144f67d031/DISS-9eb4460f-9f3a-575c-e044-00144f67d031_DISS-9eb4460f-9f3a-575c-e044-00144f67d031.html; http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eae058-ddea-203e-e044-00144f67d031/DISS-9eae058-ddea-203e-e044-00144f67d031_DISS-9eae058-ddea-203e-e044-00144f67d031.html.

²³⁷ All fields indicate that the registrant considers data for all endpoints as conclusive but not sufficient for classification.

²³⁸

http://nanopartikel.info/cms/lang/en/Wissensbasis/Aluminiumoxide/template/element2Category2ContainerList?catTitle=Exposure&containerID=534&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Aluminiumoxide/element2Category2ContainerList/ContentContainer_534

²³⁹

<http://nanopartikel.info/cms/lang/en/Wissensbasis/Aluminiumoxide>

2.7. Iron oxides: Diiron trioxide (ferric oxide, hematite, Fe₂O₃, EC Number 215-168-2) and triiron tetraoxide (ferrous-ferric oxide, magnetite, Fe₃O₄, EC Number 215-277-5)

There are several types of nanoform iron oxides. According to SRI, the most common ones are nanoform hematite (ferric oxide or Fe₂O₃) and nanoform magnetite (ferrous-ferric oxide or Fe₃O₄).

The substance diiron trioxide has been registered under REACH.²⁴⁰ However, the registration is unspecific to the nanoform (although certain references could be interpreted as referring to the nanoform). It has not been classified as hazardous.²⁴¹ The substance triiron tetraoxide has been registered under REACH.²⁴² However, the registration is unspecific to the nanoform (although certain references could be interpreted as referring to the nanoform). It has been partly classified as hazardous with the following hazard statement (GHS): H251: Self-heating: may catch fire.²⁴³

Iron oxide nanoparticles show a low level of toxicity, although production of inflammatory factors observed in some studies.²⁴⁴

According to SRI, industry sources believe that the global market for iron oxide nanoparticles is currently about €20-40 million, which should correspond to roughly 100 tonnes. This value should however be taken with caution because it is difficult to distinguish between bulk and nanoform applications of iron oxides. Nanoform ferric oxide particles are used in pigment applications (e.g. in automotive industry or in cosmetics) offering clean shades of a number of colours but with high transparency while still offering protection from UV light. Magnetite particles have been used for a long time for data storage in magnetic tapes, hard drives etc. There is a trend to use smaller particles including nanoparticles for these uses. Another use of magnetite nanoparticles is ferrofluids, which are stable colloidal suspensions of magnetic nanoparticles in a liquid carrier. Ferrofluids are used e.g. in electronic components like loudspeakers and hard disks (preventing dirt particles from entering the hard drive), or in shock absorbers in the automotive industry. Other emerging applications of nanoform iron oxide particles are in medicine. After selectively attaching nanoparticles to tumour cells, those cells can selectively be destroyed by applying electromagnetic energy. Drugs and diagnostic agents attached to magnetic nanoparticles could selectively be transported to targets in the body. Other uses of iron oxide nanoparticles include polishing media, catalysts, components

²⁴⁰ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb9b2bd-9dfd-0981-e044-00144f67d031/DISS-9eb9b2bd-9dfd-0981-e044-00144f67d031_DISS-9eb9b2bd-9dfd-0981-e044-00144f67d031.html.

²⁴¹ Except for: Acute toxicity – dermal; Acute toxicity – inhalation; Respiratory sensitization; Aspiration hazard; Reproductive toxicity; Effects via lactation (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁴² Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea4fafe-9d48-4fe0-e044-00144f67d031/DISS-9ea4fafe-9d48-4fe0-e044-00144f67d031_DISS-9ea4fafe-9d48-4fe0-e044-00144f67d031.html.

²⁴³ Except for the classification as self heating and except for: Acute toxicity – dermal; Acute toxicity – inhalation; Respiratory sensitization; Aspiration hazard; Reproductive toxicity; Effects via lactation (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁴⁴ http://nanopartikel.info/cms/lang/en/Wissensbasis/Eisen/template/element2Category2ContainerList?catTitle=Exposure&containerID=396&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Eisen/element2Category2ContainerList/ContentContainer_396

in fuel cells, oxygen sensors, ceramics and optoelectronic devices, and soil and groundwater remediation and water treatment.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Except in medical applications and cosmetics, exposure to humans and the environment at the use stage is estimated to be rather low as the iron oxide is mostly embedded in a matrix and applications do not seem to imply an intended release. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles. Specific exposure could also arise in applications for soil and groundwater remediation as well as water treatment.

2.8. Cerium dioxide (CeO₂, EC-Number 215-150-4)

Ceria (CeO₂) is a rare-earth oxide with specific optical properties.

The substance cerium dioxide has been registered under REACH.²⁴⁵ The registrant has indicated that the substance has a nanoform and has provided separate information on the nanoform. Neither form has been classified as hazardous.²⁴⁶

Inflammatory responses to cerium dioxide nanoparticles at high doses have been observed in vitro for certain cell lines, though not for others.²⁴⁷

According to SRI, the global market for nanoform cerium oxide is around 10 thousand tonnes. Nanostructured CeO_{2-x} films are used in applications in optical, electro-optical, microelectronic and optoelectronic devices. Nanoform ceria is used inter alia as a polishing material for glass surfaces and silicon wafers, to finish photomasks and disk drives, as an anti-corrosion material, e.g. in exterior architectural paint, steel and other metal plates, and in fuel cells. Another major application is as a catalytic diesel fuel additive, decreasing toxic diesel emissions and increasing fuel efficiency.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Except in applications as a fuel additive, exposure to humans and the environment at the use stage is estimated to be rather low. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

²⁴⁵ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-a217355e-db00-127d-e044-00144f67d031/DISS-a217355e-db00-127d-e044-00144f67d031_DISS-a217355e-db00-127d-e044-00144f67d031.html.

²⁴⁶ Bulk form: Except for: Respiratory sensitization; Aspiration hazard; Effects via lactation; carcinogenicity; hazardous to the ozone layer (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification; Nanoform: except for: Skin corrosion / irritation; Germ cell mutagenicity; Hazardous to the aquatic environment (both acute/short-term and long-term) (conclusive but not sufficient for classification), the registrant indicates that data for all other endpoints are lacking.

²⁴⁷

http://nanopartikel.info/cms/lang/en/Wissensbasis/Cerdioxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=67&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Cerdioxid/element2Category2ContainerList/ContentContainer_67

2.9. Zirconium dioxide (ZrO₂, EC-Number 215-227-2)

Ceramic materials made by sintering nanoform zirconia (ZrO₂) powder have a number of unique properties, including some forms with very high fracture toughness.

The substance zirconium dioxide has been registered under REACH.²⁴⁸ However, the registration is unspecific to the nanoform. It has not been classified as hazardous.²⁴⁹

In vitro tests showed stress on human lung epithelial cells at high doses.²⁵⁰

According to SRI, total consumption of nanoform zirconium dioxide is estimated to be in the range of 2,500-3,000 tonnes. The largest application, with about 50% is in optical connectors, followed by fuel cells, lithium-ion batteries, catalysts and ceramic membranes. Other developing applications are in structural and electronic ceramics, dental fillings, prostheses, fluorescent lighting and as polishing agent.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage is estimated to be low, as in most applications it is fixed in a matrix. An exception is the application in biomedical implants, where wear can lead to the generation of nanoscale debris. One of the advantages of ceramic implants is the lower release of wear debris as compared to polymer or metal components. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

2.10. Other oxide nanomaterials

Other oxide nanomaterials on the market include barium titanate, barium sulphate, strontium titanate, strontium carbonate, indium tin oxide (ITO) and antimony tin oxide (ATO). Barium titanate powders are the dominating raw material for the production of ceramic dielectric layers in low-temperature multilayer ceramic capacitors (MLCC). According to SRI, it is marketed in annual quantities of 15000 tonnes globally. Indium tin oxide is a semi-conducting material used as thin-film material for the production of transparent electrodes in liquid crystal displays, touch screens, organic LEDs, thin-film solar cells, semiconducting sensors etc. Due to its IR-radiation reflectivity it is often used as thermal insulation coating on window glass. Its anti-static properties make it additionally suitable e. g. for packing and storage of sensitive electronic components. However, as ITO-prices have drastically increased due to a global indium production shortage within the last years, research for alternatives has intensified. Antimony tin oxides have similar IR-radiation reflectivity properties. Among these materials, only the substances barium sulphate and strontium carbonate have been

²⁴⁸ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d7012e-917c-6fad-e044-00144f67d031/DISS-97d7012e-917c-6fad-e044-00144f67d031_DISS-97d7012e-917c-6fad-e044-00144f67d031.html.

²⁴⁹ Except for: Acute toxicity – dermal; Respiratory sensitization; Aspiration hazard; Effects via lactation; carcinogenicity; hazardous to the ozone layer (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁵⁰

http://nanopartikel.info/cms/lang/en/Wissensbasis/Zirkoniumdioxid/template/element2Category2ContainerList?catTitle=Exposure&containerID=591&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Zirkoniumdioxid/element2Category2ContainerList/ContentContainer_591

registered under REACH (both unspecific to nanomaterials).²⁵¹ They have not been classified as hazardous.²⁵² There are also other similar oxides but less information is available to what degree these oxides are already on the market.

For further oxides which have been registered under REACH, there is information that nanoforms exist, and certain information in the registration dossier could be interpreted as referring to the nanoform. These substances include²⁵³ dibismuth trioxide, nickel monoxide and disilver oxide.

There is also information on the existence of other nanoforms of oxides, e.g. a wide range of rare earth oxides. Most of those substances, if at all, are marketed only at smaller scale.

2.11. Calcium Carbonate (CaCO₃, EC-Number 207-439-9)

Most of the fine-ground calcium carbonate is generally in a particle size above 100 nm. There are however also nanoforms of this material, although it is difficult to get a full picture of the use of the nanoform. It seems that ultrafine calcium carbonate is used as an advanced filler in sealants and in plastic for window frames.²⁵⁴ Fine-ground calcium carbonates are widely used as fillers in paper, plastics, paints and coatings, and adhesive and sealants. They are also used as a food additive (E 170). In the latter cases, most of the material used seems however to be in a particle size above 100 nm.

The substance calcium carbonate has been registered under REACH.²⁵⁵ The registrant has indicated that the substance has a nanoform and has provided separate information on the nanoform. Calcium carbonate, including its nanoform, has not been classified as hazardous.²⁵⁶ EFSA has recently given a scientific opinion on re-evaluation of calcium carbonate (E 170) as a food additive.²⁵⁷ This opinion, concluded that *“the available data are sufficient to conclude that the current levels of adventitious nanoscale material within macroscale calcium carbonate would not be an additional toxicological concern”*.²⁵⁸

²⁵¹ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d78296-bd48-13fd-e044-00144f67d031/DISS-97d78296-bd48-13fd-e044-00144f67d031_DISS-97d78296-bd48-13fd-e044-00144f67d031.html; http://apps.echa.europa.eu/registered/data/dossiers/DISS-9876be4a-cbe0-274b-e044-00144f67d031/DISS-9876be4a-cbe0-274b-e044-00144f67d031_DISS-9876be4a-cbe0-274b-e044-00144f67d031.html.

²⁵² For both substances, all fields indicate that the registrant considers data for all endpoints as conclusive but not sufficient for classification.

²⁵³ This list is not exhaustive. In addition, there are also reaction masses between different oxides, which are not listed here.

²⁵⁴ <http://www.observatorynano.eu/project/filesystem/files/Construction%20-%20Adhesive%20%20Sealants%20-%202010.pdf>

²⁵⁵ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d91307-32ca-6360-e044-00144f67d031/DISS-97d91307-32ca-6360-e044-00144f67d031_DISS-97d91307-32ca-6360-e044-00144f67d031.html.

²⁵⁶ Both bulk and nanoform: Except for: Respiratory sensitization; Aspiration hazard; Effects via lactation (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁵⁷ <http://www.efsa.europa.eu/en/efsajournal/pub/2318.htm>

²⁵⁸ The share of particles with a size less than 100 nm in food grade calcium carbonate is estimated at less than 1%.

2.12. Other non-oxide inorganic non-metallic nanomaterials

Substances in this category which have nanomaterial forms include e.g. aluminium nitride, silicon nitride, titanium nitride, titanium carbonitride, tungsten carbide, tungsten sulphide. Among those substances, only the substance tungsten carbide has been registered under REACH.²⁵⁹ However, the registration is unspecific to the nanoform. It has not been classified as hazardous.²⁶⁰ Aluminium nitride is used in the electronic industry in various particle sizes, including nanoparticles. Titanium nitride powders with a particle size from nano- to micrometers are used as additive in the production of wear-resistant sintered materials. Furthermore it is added to plastics, particularly to PET. TiN nanoparticles improve the thermal properties of the material and allow increasing the production output of PET bottles.²⁶¹ The nanoform has been assessed by EFSA²⁶² and authorised as a food contact material.²⁶³ In vitro tests show cytotoxic effects at high doses.²⁶⁴ Tungsten carbide is used mainly for hardening the surfaces of cutting tools to improve wear and temperature resistance. Tungsten carbide nanoparticles are at the barrier to large-scale production. Tungsten sulphide seems to be a promising lubricant for harsh conditions.

3. METALS AND METAL ALLOYS²⁶⁵

3.1. Gold (Au, EC-Number 231-165-9)

According to SRI, the global production of colloidal gold dispersions in 2010 corresponded to an equivalent to 3.5 kilograms of gold. Gold nanoparticles are mostly used in medical applications, in particular in *in-vitro*-diagnostics. Other applications include catalysts, optics, solar cells, inks for printable electronics, sensors and surface coatings.

Among the few available studies, results on toxicity of gold nanoparticles seem to be somewhat contradictory but there are indications of inflammatory responses (in particular for smaller particle sizes). Gold nanoparticles can become systematically available following exposure and tend to accumulate in the liver (but to an extent also other organs).²⁶⁶

²⁵⁹ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea8a704-db22-007b-e044-00144f67d031/DISS-9ea8a704-db22-007b-e044-00144f67d031_DISS-9ea8a704-db22-007b-e044-00144f67d031.html.

²⁶⁰ Except for: Respiratory sensitization; Effects via lactation; Carcinogenicity (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁶¹ <http://nanopartikel.info/cms/lang/en/Wissensbasis/Titannitrid>

²⁶² <http://www.efsa.europa.eu/en/efsajournal/pub/888.htm>

²⁶³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:012:0001:0089:EN:PDF>; for scientific opinion, see: http://www.efsa.europa.eu/en/scdocs/doc/cef_op_ej888-890_21stlist_en,3.pdf

²⁶⁴

http://nanopartikel.info/cms/lang/en/Wissensbasis/Titannitrid/template/element2Category2ContainerList?catTitle=Exposure&containerID=768&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Titannitrid/element2Category2ContainerList/ContentContainer_768

²⁶⁵ Note that alloys are not substances but special mixtures for the purpose of REACH.

²⁶⁶ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 354; http://nanopartikel.info/cms/lang/en/Wissensbasis/gold/template/element2Category2ContainerList?catTitle=Exposure&containerID=692&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/gold/element2Category2ContainerList/ContentContainer_692.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage can be substantial in certain biomedical applications. In most others, it is estimated to be relatively low because the nanoparticles are bound in a matrix. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

3.2. Silver (Ag, EC-Number 231-131-3)

Nanosized silver was first produced in 1880. It was used for a long time in photographic film applications. Today, it is mostly used in antimicrobial applications where a high release of silver ions is needed (in other applications, bulk silver or silver salts are used).

The substance silver has been registered under REACH.²⁶⁷ Despite a number of references to tests relating to nanoforms, there is an explicit statement that the nanoform is not covered by the dossier. Silver powder has been classified as hazardous (Aquatic Chronic 1 and Aquatic Acute 1) with the following Hazard Statements (GHS): H410: Very toxic to aquatic life with long lasting effects and H400: Very toxic to aquatic life.²⁶⁸

Silver nanoparticles show various adverse health effects at high doses. At very high doses, they can provoke pulmonary oedemas and brown stains in skin and body organs (argyria). There are indications that silver nanoparticles can penetrate skin, become systematically available following exposure and tend to accumulate in the liver (but to an extent also other organs).²⁶⁹ Silver is known as a highly ecotoxic metal, in particular for the aquatic environment. This seems to be linked to the toxicity of the silver ion. However, there are also studies which show higher effects from silver nanoparticles than what might be expected from the presence of ions alone.²⁷⁰ There are also concerns on the possible development of antimicrobial resistance due to increased use of nanosilver, as well as possible adverse effects on waste water treatment processes. The Commission has recently issued a mandate to SCENIHR to assess safety, health and environmental effects of nanosilver and its role in antimicrobial resistance.²⁷¹

According to SRI, the global market for nanoform silver in antimicrobial uses is estimated at 22 tonnes (around 10% of total use of silver for antimicrobial use). Antimicrobial uses of nanoform silver include anti-microbial textiles for hospitals, wound plasters, and anti-odour sportswear, bed mattresses, socks or underwear. There are also reported uses in toys, household appliances such as refrigerators and washing machines, cosmetics, containers for contact

²⁶⁷ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d92ea78-89c7-2334-e044-00144f67d249/DISS-9d92ea78-89c7-2334-e044-00144f67d249_DISS-9d92ea78-89c7-2334-e044-00144f67d249.html.

²⁶⁸ Except for the classification as Aquatic Chronic 1 H410: Very toxic to aquatic life with long lasting effects and except for: Reproductive toxicity; Effects via lactation, Carcinogenicity; Hazardous to the aquatic environment (acute/short-term) (data lacking), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁶⁹ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 354; http://nanopartikel.info/cms/lang/en/Wissensbasis/Silber/template/element2Category2ContainerList?catTitle=Exposure&containerID=192&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Silber/element2Category2ContainerList/ContentContainer_192.

²⁷⁰ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 358.

²⁷¹ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_q_027.pdf

lenses, etc. A much lower amount (in the range of 200 kg) went into non-textile antimicrobial coatings. Other uses of nanoform silver in small quantities include inks for inkjet printers and printable electronics, catalysts, photovoltaics, displays and fuel cells.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage can be significant for antimicrobial applications. For other applications, it is considered to be low because it is bound in a matrix. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

3.3. Other metallic nanoparticles

Platinum and palladium alloy nanoparticles are mostly used in electronics (production of multi-layer ceramic capacitors). According to SRI, quantities reported are in the range of 12 tonnes annually (including sizes above 100 nm). Other uses include catalysis (including combustion exhaust purification) and energy technologies. Uses in data storage and medical applications are being discussed.

Copper nanopowders (though mostly in sizes above 100 nm) are used in electronics and, to a small degree, in inks. Copper nanoparticles are highly toxic to the aquatic environment.²⁷²

Iron nanoparticles are mostly used in magnetic recording tapes (needle shaped ferrite particles), though this use is declining.

Titanium nanoparticles are increasingly used as an alloy compound in lightweight materials within the aerospace and increasingly the automotive sector, and as a material for medical implants.²⁷³

There are also **other metal nanoparticles (e.g. nickel, cobalt, aluminium, zinc, manganese, molybdenum, tungsten, lanthanum, lithium)** used in smaller quantities, e.g. in electronics, though it is not always clear to what degree the particles are below 100 nm. Rhodium nanoparticles are reported to be used in catalysts.²⁷⁴

4. CARBON-BASED NANOMATERIALS

4.1. Fullerenes

Fullerenes are molecules consisting of an even number of 60 or more carbon atoms, which form a cage-like fused-ring polycyclic system with 12 5-membered rings and the rest 6-membered rings (see <http://cdb.iso.org>). The simplest molecule with 60 carbon atoms is spherical with a diameter of around 0.71 nm.²⁷⁵

²⁷² Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enrhres-final-report>, p. 358.

²⁷³ ObservatoryNano <http://www.observatorynano.eu/project/document/63/>;
<http://www.observatorynano.eu/project/document/66/>

²⁷⁴ <http://www.rivm.nl/bibliotheek/rapporten/340370001.pdf>, p. 22.

²⁷⁵ Nucleus to nucleus in a crystalline structure of C₆₀ molecules.

The studies conducted so far suggest oxidant driven responses in the lungs (inflammation, cytotoxicity and tissue damage). There are limited ecotoxicological studies which indicate possible aquatic toxicity. However, some of the results may also be due to the solvents used.²⁷⁶

Despite substantial research and development activities, the current market for fullerenes and derivatives is supposed to be relatively small, including additives for polymers used in sports equipment such as tennis rackets and golf balls (strength), cosmetics (dark color, anti-aging skin creams), in fuel cells, lithium battery anodes, solar cells component, protective eyewear etc. There is also significant research, e.g. into medical applications.

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage can be significant in particular for cosmetics and biomedical applications. For other applications, it is considered to be low because it is bound in a matrix. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

4.2. Carbon nanotubes and carbon nanofibers²⁷⁷

Carbon nanotubes are tubes consisting of one or more concentric sheets of carbon atoms arranged in the same way as the carbon atoms in ordinary graphite. In the case of single walled carbon nanotubes, the tube diameter is close to 1 nm. Multi-walled carbon nanotubes consist of several such tubes in each other (similar to a Russian doll but made out of tubes). Depending on the structure of the tube, they may exhibit very high thermal and electric conductivity and a high strength-to-weight ratio.

The substance multi-walled carbon nanotubes has been registered under REACH.²⁷⁸ The registrant has indicated that the substance is a nanomaterial. It has not been classified as hazardous.²⁷⁹ There is another registration of multi-walled carbon nanotubes under graphite.²⁸⁰ The registrant has indicated that the substance is a nanomaterial. It has been

²⁷⁶ EU-OSHA, Workplace exposure to nanoparticles, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view; Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 353; http://nanopartikel.info/cms/lang/en/Wissensbasis/Fullerene/template/element2Category2ContainerList?catTitle=Exposure&containerID=353&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/Fullerene/element2Category2ContainerList/ContentContainer_353.

²⁷⁷ In principle, carbon nanotubes are a special type of carbon nanofibres. However, sometimes the term “carbon nanotubes” is used to characterise the thinner carbon fibres, whereas the term “carbon nanofibres” is used for the thicker variants.

²⁷⁸ Public information available on: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-b281d1a0-c6d8-5dcf-e044-00144f67d031/DISS-b281d1a0-c6d8-5dcf-e044-00144f67d031.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-b281d1a0-c6d8-5dcf-e044-00144f67d031/DISS-b281d1a0-c6d8-5dcf-e044-00144f67d031_DISS-b281d1a0-c6d8-5dcf-e044-00144f67d031.html).

²⁷⁹ Except for: Respiratory sensitization; Effects via lactation; hazardous to the ozone layer (data lacking), all other fields indicate that the registrant considers data for all endpoints as conclusive but not sufficient for classification.

²⁸⁰ [http://apps.echa.europa.eu/registered/data/dossiers/DISS-abda73cd-a2cd-3801-e044-00144f67d249/DISS-abda73cd-a2cd-3801-e044-00144f67d249.html](http://apps.echa.europa.eu/registered/data/dossiers/DISS-abda73cd-a2cd-3801-e044-00144f67d249/DISS-abda73cd-a2cd-3801-e044-00144f67d249_DISS-abda73cd-a2cd-3801-e044-00144f67d249.html)

classified as hazardous with the following Hazard Statements (GHS): H319: Causes serious eye irritation; and H335: May cause respiratory irritation.²⁸¹

In some studies, lung toxicity (inflammation, cytotoxicity and tissue damage) was observed after carbon nanotube exposure. There are indications that there are variations between different types of carbon nanotubes, with single walled carbon-nanotubes often being shown to be more toxic than multi-walled carbon nanotubes, and longer length (> 20µm) resulting in greater pathogenicity. Some animal studies detected that specific modifications of carbon nanotubes showed effects similar to that of asbestos.^{282,283} Some of the observed effects may also be driven by metal contaminations.

According to SRI, the market of carbon nanotubes (thinner than 20 nm) worldwide is estimated around 200-250 tonnes (€30-40 million, mostly multi-walled carbon nanotubes) in 2009. The largest use is as a product imparting electrical conductivity to plastic materials, e.g. in disk drive components or automotive plastic fuel lines and fenders (electrostatic coatings). Other uses include polymer additives, paints and coatings, fuel cells, electrodes, electrolytes and membranes in batteries, especially in miniature lithium batteries. There is a lot of research and development into new applications, including into “in-situ component use” which might in term complement and expand the use of silicon in electronics.

According to SRI, the market for carbon nanofibres in the thickness range between 20 to several 100 nm is estimated at around 300-350 tonnes (€50-60 million) in 2009. There is a strong increase of use of nanofibres in lithium ion batteries which is by far the largest application. Other uses include fuel cells, fabrics for filtration or in plastic compounds for fuel lines.

There are also significantly higher estimates in terms of marketed volumes of carbon nanotubes, nanofibers, fullerenes and POSS (around 3500 tonnes annually).²⁸⁴

Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Measurements of airborne CNTs in workplaces in research and industrial settings have shown a likely exposure of workers in some cases. Higher levels of airborne CNTs were found in particular where processes such as extrusion and cutting of bags containing nanomaterials, dry-sawing of

²⁸¹ Except for the classification as Eye Irrit. 2 H319: Causes serious eye irritation; and STOT Single Exp. 3 H335: May cause respiratory irritation., and except for: Respiratory sensitization; Aspiration hazard; Reproductive toxicity; Effects via lactation; hazardous to the ozone layer (data lacking); and carcinogenicity (inconclusive), all other fields indicate that the registrant considers data for all other endpoints as conclusive but not sufficient for classification.

²⁸² EU-OSHA, Workplace exposure to nanoparticles, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view; Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, p. 353; http://nanopartikel.info/cms/lang/en/Wissensbasis/kohlenstoffnanoroehrchen/template/element2Category2ContainerList?catTitle=Exposure&containerID=165&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/kohlenstoffnanoroehrchen/element2Category2ContainerList/ContentContainer_165.

²⁸³ Donaldson, K., Murphy, F. A., Duffin, R., Poland, C. A., 'Asbestos, carbon nanotubes and the pleural mesothelium: a review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma', Particle & Fibre Toxicology, Vol. 7, p. 5, 2010.

²⁸⁴ <http://www.marketresearch.com/Future-Markets-Inc-v3760/Carbon-Nanotubes-Nanofibers-Fullerenes-POSS-6542959/>

nanomaterial-containing composites took place.²⁸⁵ Exposure to humans and the environment at the use stage is considered to be low because it is bound in a matrix in most uses. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles. Impacts on recycling are also under investigation.

4.3. Carbon black (EC number 215-609-9)

Carbon black is a black powder consisting of amorphous carbon to a degree of 80-95 %. It is manufactured by controlled incomplete combustion of hydrocarbons. There are various grades with different primary particle sizes, most of them between 1 nm and 100 nm (more than 95% of global production). However, there are also grades with primary particle sizes up to 500 nm. In industrial materials, the primary particles are normally aggregated or agglomerated.

The substance carbon black has been registered under REACH²⁸⁶ (identified in one of three registration dossiers as a nanomaterial using the relevant tick-box). In one of three registration dossiers, it has been classified as hazardous (Carc. 2) with the following Hazard Statement (GHS): H351: Suspected of causing cancer; Route of exposure: Inhalation. In the other two dossiers, it has not been classified.²⁸⁷

Based on results from experimental studies²⁸⁸, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) classified carbon black as a possible carcinogen to humans.²⁸⁹

Among the few long term epidemiological studies, there are studies on respiratory health in the carbon black industry.^{290,291} In its assessment of those studies, the Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES) concluded: *“The results from the discussed epidemiology studies of the carbon black industry indicate some adverse effects of exposure to carbon black dust on respiratory health. However, the main findings are reassuring in that respiratory symptoms and lung function appear to be primarily*

²⁸⁵ Möhlmann, C. et al., “Exposure to carbon nano-objects in research and industry”, INRS Occupational Health Research Conference 2011 “Risks associated with nanoparticles and nanomaterials”, April 2011, Conference proceedings, Session II, p. 64.

²⁸⁶ Public information available on: http://apps.echa.europa.eu/registered/data/dossiers/DISS-76fd8ce3-be46-5f12-e044-00144f26965e/DISS-76fd8ce3-be46-5f12-e044-00144f26965e_DISS-76fd8ce3-be46-5f12-e044-00144f26965e.html; http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ead7c63-de5e-523a-e044-00144f67d031/DISS-9ead7c63-de5e-523a-e044-00144f67d031_DISS-9ead7c63-de5e-523a-e044-00144f67d031.html; http://apps.echa.europa.eu/registered/data/dossiers/DISS-9e9e2f65-87c3-4085-e044-00144f67d031/DISS-9e9e2f65-87c3-4085-e044-00144f67d031_DISS-9e9e2f65-87c3-4085-e044-00144f67d031.html.

²⁸⁷ Except for the classification Carc. 2H351: Suspected of causing cancer; Route of exposure: Inhalation.in one of three dossiers: and except for Effects via lactation (all three dossiers data lacking) and for Acute toxicity – dermal; Aspiration hazard; Reproductive toxicity; Germ cell mutagenicity; hazardous to the ozone layer (all one out of three dossiers: data lacking), all other fields on health and environmental hazards in the three dossiers indicate that the registrants consider data for all other endpoints as conclusive but not sufficient for classification.

²⁸⁸ Note that experimental studies are typically conducted with high doses.

²⁸⁹ International Agency for Research on Cancer – IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Carbon Black, Titanium Dioxide, and Talc*, Volume 93, (2010). Available at : <http://monographs.iarc.fr/ENG/Monographs/vol93/index.php>.

²⁹⁰ Hodgson, J.T. and Jones, R.D. 1985, A mortality study of carbon black workers employed at five United Kingdom factories between 1947 and 1980, *Archives of Environmental Health*, vol. 40, pp. 261-268.

²⁹¹ Sorahan, T., Hamilton, L., van Tongeren, M., Gardiner, K. and Harrington, J.M. 2001, A cohort mortality study of U.K. carbon black workers, 1951-1996, *Am J Ind Med*, vol. 39, pp. 158-170.

associated with current exposure rather than being caused by cumulative exposures. A mortality study by Sorahan et al. 2011 clearly indicates no strong and little suggestive evidence of excess non-malignant respiratory disease associated with working in the carbon black industry. Despite the fact that two of the five factories investigated generated evidence that there was excess mortality from lung cancer, the study has failed to link this disease to carbon black exposure.”²⁹² IARC²⁹³ also reviewed those studies, along with a number of other studies.²⁹⁴ It considered that epidemiological evidence was inconsistent and therefore concluded that there is inadequate evidence from epidemiological studies to assess whether carbon black causes cancer in humans.²⁹⁵

Several authors detected inflammation, cytotoxicity and tissue damage induced by carbon black nanomaterials in the lungs as a consequence of carbon black exposure.²⁹⁶ ²⁹⁷ Some cardiovascular effects as a consequence of carbon black exposure were also found.²⁹⁸

According to SRI, total world consumption of carbon black was estimated in 2010 at 9.6 million tonnes, with a market value of around 10 bn €. As filler material carbon black substantially increases the mechanical wear-resistance of rubber products. Around 73% of the world production goes into tyres, and another 19% into other rubber products. Further applications include pigments (toners, printer inks) and antistatic fillers for plastic packaging. There are also reported uses as mascara, flower soil, décor paper and fibres, and to manufacture electrodes and carbon brushes.²⁹⁹

Workplace exposure can occur at production, for example in rubber and tyre manufacturing, use, from abrasion and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage varies according to application but can be significant, e.g. environmental exposure due to wear of tyres.³⁰⁰ There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles.

4.4. Graphene flakes

Graphene flakes consist of a single-layer graphite sheet. They became subject of significant research since 2004, when graphene flakes were isolated through new methods, for which Andre Geim and Konstantin Novoselov were attributed the Nobel Prize in Physics for 2010.

²⁹² Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>, executive summary p. xiv.

²⁹³ International Agency for Research on Cancer, <http://www.iarc.fr/>.

²⁹⁴ <http://monographs.iarc.fr/ENG/Monographs/vol93/mono93.pdf>, p. 190.

²⁹⁵ Note that IARC classified carbon black as a possible carcinogen to humans only based on results from experimental studies.

²⁹⁶ EU-OSHA, *Workplace exposure to nanoparticles*, Luxembourg, 2009. Available at: http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view.

²⁹⁷ http://nanopartikel.info/cms/lang/en/Wissensbasis/CarbonBlack/template/element2Category2ContainerList?catTitle=Exposure&containerID=552&queryPath=/content/jahia/dana/ContentPage_3/Wissensbasis/CarbonBlack/element2Category2ContainerList/ContentContainer_552

²⁹⁸ Niwa, Y., Hiura, Y., Murayama, T., Yokode, M., Iwai, N., 'Nano-sized carbon black exposure exacerbates atherosclerosis in LDL-receptor knockout mice', *Circulation Journal: Official Journal of the Japanese Circulation Society*, 71, 2007, 1157-1161.

²⁹⁹ Last six uses: <http://nanopartikel.info/cms/lang/en/Wissensbasis/CarbonBlack>.

³⁰⁰ As part of the rubber matrix.

Graphene flakes are a semi-metal or zero-gap semiconductor. They have a very high electron mobility at room temperature, a high opacity and a number of other properties which makes them a promising material for a number of applications, even though market development is still at an early stage. Possible applications are sensors, graphene transistors, integrated circuits, electrochromic devices, transparent conducting electrodes, solar and fuel cells, antimicrobial materials, specific materials for aircraft (e.g. lightning strike protection, prevention of ice adhesion, radiation hardness) and the automotive industry (e.g. prevention of static build-up on fuel lines).

Exposure to humans and the environment is estimated to be rather low, as the material is normally fixed in a matrix in the above applications. Behaviour of graphene flakes at the end-of-life stage is still unknown.

5. NANOPOLYMERS AND DENDRIMERS

There are many nanomaterials used as an ingredient in polymers. This type of use is described under the relevant substances above.

In addition, there are specific polymeric nanoparticles, nanotubes, nanofibres, nanofilms and nanostructures. Polymers are not subject to REACH registration.³⁰¹ Dendrimers are a distinct group with specific polymeric structures. These substances are described below. Most of these substances are at an early stage of market development described applications are often still at research and development stage. Sufficiently robust data on market quantities of marketed substances could not be found.

Polymer nanoparticles are nanoscale polymeric units such as e. g. polyacetylbenzene-polydiene nanoparticles (PAB-PDM). They are used e.g. in drug delivery systems or as filler material in matrix composites.

Polymer nanotubes, nanowires and nanorods have potential applications in electronic, magnetic, optical, optoelectronic, and micromechanical devices. One of the promising polymeric nanotube types are polyaniline nanotubes (PANI) which show a good conductivity and may be used for e. g. conductive fabrics.

Polyglycidylmethacrylate (PGMA) fibres can be utilized to form fabrics and so called "smart fibres", which change their properties depending on the environmental conditions. Textiles based on PGMA fibres may switch e. g. between hydrophobic and hydrophilic, between conductive and non-conductive, between acidic and basic properties or may change colors etc.

Nanocellulose (fibrils and crystals) can be used as a reinforcement material in composites and for medical implants.³⁰²

Nanostructured polymer-films are polymeric nanoscale thin films appearing mainly as polyacetylthiophene-films, polystyrene-polyethylene oxide (PS-PEO) films or as acrylic glass (Poly(methyl methacrylate) (PMMA)) films. They are used as coatings in the bio-medical

³⁰¹ Nevertheless, in most cases, the monomers the polymer consists of must be registered. See REACH Regulation, Article 6(3), <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:en:PDF>.

³⁰² <http://nanopartikel.info/cms/lang/en/Wissensbasis/Cellulose>

sector and have the potential to be used also in other sectors. There are also other nanofilms, e.g. based on styrene-ethylene-butylene-styrene (SEBS).

Polyacrylonitrile nanostructures (PAN) give rise for utilization in semiconductors, solar cells, sensors and membranes in filters. Their electrical properties are based on a variable and controllable bandgap for semiconductor use.

Dendrimers are tree-shaped molecular structures similar to polymers. They are characterised by a high specific surface and, when dispersed, by a non-linear mass-viscosity relation. They are relatively expensive and there is not much information about the current market size. Their major applications include pharmaceuticals, light-emitting diodes and lasers, catalyst carriers, cross-linking agents in radiation-curable surface coating resin, semi-permeable membranes, polymer additives and biotechnological applications.

6. QUANTUM DOTS

Quantum dots are semiconductors whose electronic characteristics are closely related to the size and shape of the individual crystal. Typical dots are made of nanomaterials such as cadmium selenide, cadmium sulfide, indium arsenide and indium phosphide. They are applied in rather small quantities in computing, biological analysis, photovoltaic devices, light emitting devices and photodetector devices.³⁰³ The global market for quantum dots is estimated at around €55 m.³⁰⁴

7. NANOCCLAYS

Nanoclays are nanoparticles of layered mineral silicates such as montmorillonite, bentonite, kaolinite, hectorite, and halloysite. Nanoclays have uses e.g. as polymer nanocomposites, in paints, inks, greases, and cosmetics formulations, as a drug delivery vehicle, in waste water treatment³⁰⁵ and in tyres.³⁰⁶ The global market for nanoclays has been evaluated at around €150 m.³⁰⁷ Several substances which also exist as nanoclay have been registered under REACH. However, the registration dossiers are generally unspecific to nanoclays. Moreover, according to industry sources, some of the nanoclays occur in nature and thus are exempt from registration.³⁰⁸

8. NANOCOMPOSITES

There are various types of composites of nano- and non-nanomaterials. These materials are not separately described here but mentioned as possible applications of the relevant substances mentioned above.

³⁰³ http://en.wikipedia.org/wiki/Quantum_dot

³⁰⁴ <http://bccresearch.blogspot.com/2011/06/global-market-for-quantum-dots-to-grow.html>

³⁰⁵ <http://www.ias.ac.in/maternal/bmsapr2006/133.pdf>

³⁰⁶

<http://www.observatorynano.eu/project/filesystem/files/Briefing%20No.23%20Nanotechnology%20in%20Automotive%20Tyres.pdf>

³⁰⁷ <http://www.marketresearch.com/search/results.asp?query=nanoclays&submit1=Go>

³⁰⁸ <http://www.reach-centrum.org/en/consortiumslt/consortia-under-reach/organoclays-reach-consortium.aspx>

9. OTHER

There are reports on the use of nitrogen and phosphorous compounds in nanoform, used as flame retardants in textile industry and polyetherketones in nanoforms as anti-sticking coatings of pans.³⁰⁹

In addition, there are a number of substances notified under the CLP Regulation which have been identified by the notifier as nanomaterial through ticking the “nanomaterial” tickbox, for which little further information could be found on uses of the nanoform. These include manganese dioxide, divanadium pentoxide, dicopper oxide, siloxanes and silicones (see also Appendix 3).

³⁰⁹ http://www.bund.net/nc/themen_und_projekte/nanotechnologie/nanoproduktdatenbank/produktsuche/

Appendix 3

ECHA Analysis of Information on Nanomaterials retrieved in the ECHA Databases for REACH Registrations and CLP Notifications received by the end of June 2011

This appendix is based solely on the content of the databases at the end of June 2011. Any registration or notification received after this has not been systematically screened for information on nanomaterials. It is therefore possible that more registrations and notifications concerning nanomaterials have been received after this date. For example, two registrations were received for multi-walled carbon nanotubes at the end of July 2011.

Executive Summary

The REACH registration and CLP databases maintained by ECHA were screened for those registrations and notifications that include information on nanomaterials. This involved doing a free-text search for “nano” in all machine readable fields in all registration and notifications stored in the database. In addition all files attached to registrations were screened. “Nano” was chosen as the definite search-term for the screening as there is no definition for nanomaterial in REACH or CLP nor guidelines on how to report information on size for nanomaterials. The use of “nano” by a registrant/ notifier in a relevant context was considered to be an indication that the dossier may include nanomaterials or nanoforms within the scope of the registered/notified substance.

Screening of the REACH registration database at the end of June 2011 yielded a list of 78 registered substances that include information on nanomaterials from the ca. 4,700 substance registrations stored in REACH registration database. Of these 78, three substance registrations had explicitly selected “nanomaterial” as the form of the substance. Two substance registrations included possibly relevant information but had not selected “nanomaterial” as the form of the substance. Six substance registrations included “nano” in the description of the registered substance but where the registrant referred to the substance as being nano-structured rather than a nanomaterial. Eight specifically excluded nanoforms from the scope. For the vast majority of substances (59 of the 78 substances listed), “nano” was found solely in the context of read-across from studies performed on nanoforms of the registered substance and it cannot be definitely concluded based on the information included in the respective dossiers whether or not nanoforms are within the scope of the registered substance.

Screening of ca. 3.2 million notifications stored on the CLP notification database at the end of June 2011 yielded a list of 18 notifications where “nanomaterial” was selected as the form of the substance, one of which had included “nano” in both the chemical and EC name fields. An additional three notifications had included “nano” in the chemical name field.

The list of substances retrieved from the REACH and CLP databases using this strategy and clearly including nanoforms within the scope of the substance are reported in Annexes 2 and 3 of this report. It should be noted that the screening employed will not find those substances that include nanoforms but where “nano” was not included in any field of the respective registrations and notifications or in any file attached to the registrations. However, as registrants and notifiers were encouraged to use “nano” as the prefix for any composition, analytical data and information requirement that referred to the nanoform, we are confident

that we have retrieved those substances where registrants/notifiers wished to explicitly include information on nanoforms.

Based on the screening of the databases at the end of June 2011, it can be concluded that three registered substances from the REACH registration database that includes ca. 26,000 registrations for ca. 4,700 substances and 18 CLP notifications from the ca. 3.2 million notifications in the CLP database had selected “nanomaterial” as the form of the substance in the respective registrations and notifications. One substance was common to both lists. It should be noted that registrants include classification and labelling information in their respective registration dossiers and thus are not required to make a separate CLP notification for that substance. Thus the CLP notified substances on the list refer to those substances that are not currently registered by the party making the notification.

The following report describes how ECHA retrieved information on nanomaterials stored in the ECHA databases for REACH registrations and CLP notifications. It details the basis for this action and describes the content of the ECHA databases in terms of what information is required to be reported according to specific deadlines for the applicable legislation and the format in which this information is stored. The absence of specific requirements for nanomaterials in both the REACH and CLP legislations is also discussed. A detailed summary of the screening strategy undertaken to retrieve information from the databases is included together with the results.

1. BASIS FOR THE COMPILATION OF A LIST OF SUBSTANCES THAT INCLUDE INFORMATION ON NANOMATERIALS IN THE REACH AND CLP DATABASES

In 2010, the Commission made an official request to ECHA for assistance in the preparation of the REACH and CLP aspects mentioned in the 2nd Commission communication on the Regulatory aspects of nanomaterials.³¹⁰ The request from the Commission was to compile information on nanomaterial types and uses, including safety aspects, which has been reported by the chemical companies either in their registration dossiers submitted under the REACH³¹¹ Regulation or in notifications to the Classification and Labelling Inventory submitted under the CLP Regulation.³¹² This commitment was included in the ECHA workplan for 2011 under main outputs for “*Activity 7: Scientific and technical advice to EU institutions and bodies: Report compiled for the Commission by 30 June containing information on registered nanomaterials*”.

2. DESCRIPTION OF THE REACH AND CLP DATABASES HELD BY ECHA

ECHA is the responsible EU agency for the implementation of both the REACH and CLP regulations. The REACH regulation which came into force on the 1 June 2007 requires manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment (Article 1(3) of REACH) and is applicable to substances in whatever size or form. To comply with the regulation, manufacturers and importers are required to submit Registration dossiers

³¹⁰ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0366:FIN:en:PDF>

³¹¹ REACH: Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals.

³¹² Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures.

to ECHA including detailed information on their substances as defined in the REACH legal text. The CLP regulation obliges manufacturers, importers and downstream users to classify substances and mixtures placed on the market. This regulation explicitly requires these parties to consider the forms or physical states in which the substance or mixture is placed on the market and in which it can be reasonably be expected to be used (CLP Art 9(5)) when evaluating the available information for classification. To fulfil this obligation, CLP notifications including classification and labelling information defined in the CLP Regulation are required to be submitted to ECHA. Deadlines for submission of REACH registration and CLP notification dossiers to ECHA are defined in the respective regulations and are typically both tonnage and hazard profile specific.

Since 1 June 2008, ECHA has received more than 26,000 REACH registrations for approximately 4700 distinct substances (7 March 2011) and more than 3.2 million CLP notifications for approximately 109,000 distinct substances (1 April 2011). The tiered REACH registration deadlines for existing (or phase-in) chemicals mean that the registrations received by the 1 December 2010 deadline refer to those substances that are manufactured or imported per legal entity at > 1000 tons per year and those that are classified as carcinogenic, mutagenic or toxic to reproduction (CMR) or have a classification R50/53 that are manufactured per legal entity at greater than 1 and 100 tonne /year respectively. New substances manufactured or imported after REACH came into force on 1 June 2007 are required to be registered when their tonnage exceeds 1 ton /year. The requirement to make a CLP notification by the 3 January 2011 deadline refers to substances placed on the market at > 1 ton per year and substances classified as hazardous under CLP and present in a mixture above the concentration limits specified in Annex I to CLP or in Directive 1999/45/EC which results in the classification of the mixture as hazardous irrespective of tonnage.

These REACH registrations and CLP notifications are stored in databases maintained by ECHA. ECHA therefore has a very large repository of registration and notification dossiers that can in principle provide information on nanomaterials registered or notified and therefore on the market. Following the request from DG ENTR and DG ENV, ECHA has searched these received registration and notification dossiers for those that include information on nanomaterials and this report details the information found in the dossiers to date.

3. APPLICATION OF REACH AND CLP REQUIREMENTS FOR NANOMATERIALS

It is important to note that neither the REACH nor CLP regulations have any specific requirements for registrants and notifiers of substances that are nanomaterials or nanoforms of a substance nor is there a definition for nanomaterial in the REACH and CLP regulations. The European Commission addressed this in a series of papers endorsed by the REACH competent authorities. In document CA/59/2008 rev.1 “Nanomaterials under REACH”³¹³, it was clarified that nanomaterials are covered by the definition of substance under REACH and that REACH requirements are applicable to nanomaterials even though there are no specific provisions in the legal text for nanomaterials. It was agreed that nanomaterials could be considered as either substances in their own right and thus registered as such or as forms of a substance and included in the registration dossier of corresponding bulk substance. In both cases, the respective registration dossier should include all relevant information on the nanomaterial. The phase-in status of nanomaterials was also addressed and it was agreed that

³¹³ <http://ec.europa.eu/environment/chemicals/reach/pdf/nanomaterials.pdf>

their status as existing chemicals would depend on the registration strategy adopted by the registrant; nanomaterial substances are considered to be phase-in when listed on EINECS and pre-registered appropriately and nanoforms of a bulk substance are considered to be phase-in when the bulk substance is listed on EINECS and appropriately pre-registered.

For CLP notifications, document CA/90/2009 Rev. 2 “Classification, labelling and packaging of nanomaterials in REACH and CLP”³¹⁴ states that classification and labelling of nanomaterials should follow the rules set in the CLP regulation and that it should be done on a case-by-case basis giving due consideration to relevant available data. It was considered vital that the notifier evaluates whether changes in size, form or physical state influence hazardous properties. It was noted that a separate notification may be required for the nanoform of a bulk substance when the available data on the intrinsic properties indicates a difference in hazard class.

There was therefore the expectation that the nanoform be reported in the dossier as any other form of the substance together with information on its hazardous properties and the risk management measures to handle the risk, whenever appropriate. Registrants and notifiers were encouraged to make explicit in their dossiers if they believed their substance was a nanomaterial or a nanoform of a substance.

REACH registration dossiers are submitted in IUCLID format to ECHA. IUCLID refers to the software application that enables registrants to store data on chemicals and to prepare and submit dossiers. To aid REACH registrants to include information on nanomaterials in their dossiers, ECHA prepared a technical IUCLID manual “Nanomaterials in IUCLID 5.2”³¹⁵ where registrants were provided with practical instructions on the available IUCLID fields for nanomaterials and on how to ensure that information included was readily retrievable. For example, the manual highlighted the new specific fields (picklists) available in IUCLID 5.2 (release data 15 February 2010) where registrants could select “nanomaterial” as a form of the substance in the information requirements for “form of the substance” and in the classification and labelling sections of their dossiers. The manual also provided technical instructions on how to identify substances as nanomaterials and/or include nanoforms as different substance compositions in submitted registration IUCLID dossiers.

CLP notifications could be submitted as IUCLID dossiers or via an on-line tool in REACH-IT. For submissions in either IUCLID format or via the on-line tool, the option to select nanomaterial was also available for “form of the substance” under classification and labelling.

4. SUMMARY OF THE SCREENING STRATEGY FOR RETRIEVING INFORMATION ON NANOMATERIALS INCLUDED IN REACH AND CLP DOSSIERS

The strategy adopted for retrieving information stored in REACH registrations and CLP notifications was based on how the information is stored in the respective databases.

REACH registration database: REACH registration dossiers are stored in the IUCLID database maintained by ECHA. Information can be retrieved from the dossiers by ECHA and member state competent authorities (MSCAs) by IUCLID query tools or via REACH-IT. For the purpose of this exercise, a combination of standard IUCLID query tools for retrieving

³¹⁴ http://ec.europa.eu/environment/chemicals/reach/pdf/classif_nano.pdf

³¹⁵ <http://iuclid.echa.europa.eu/index.php?fuseaction=home.documentation#technicalmanual>

information from IUCLID dossiers and other search tools developed in-house were used to identify those dossiers that included information on nanomaterials in any IUCLID text-field or any file attached to the dossier.

The screening strategy for REACH registration database is summarised as follows:

- Retrieve those dossiers that selected “nanomaterial” as form of the substance in the respective fields available
- Retrieve those dossiers who reported the nanoform as a separate composition of the substance in the appropriate section of the dossier
- Free-text searching of all fields in all IUCLID dossiers in the ECHA IUCLID database
- Free-text searching of all files attached to all IUCLID dossiers in the database (files attached include the CSR, analytical information relevant for substance identification and any other relevant information the registrant wishes to include to fulfil an information requirement)

The four screening steps were undertaken independently of each other and the lists of substances retrieved were cross-correlated with each other. The implications of the obligation to submit a joint REACH registration per substance and based on tonnages/hazard class are briefly outlined in Annex 1 as this determines how information is stored in the database and when such information is available to ECHA.

CLP notification database: all CLP notifications received are stored in the REACH-IT database and can be screened using IT tools developed specifically for this purpose.

The screening strategy for the CLP notification database is summarised as follows:

- Retrieve those notifications that selected “nanomaterial” as form of the substance in the specific field available for this purpose
- Free-text searching of all searchable fields in the notifications (i.e. mainly substance identity-related fields)

Choice of search term: “nano” was chosen as the definite search-term for screening for information on nanomaterials/nanoforms of a substance in registration and CLP dossiers. As there is no definition for nanomaterial in REACH or CLP nor guidelines on how to report in the dossiers information on size for nanomaterials, this ruled out using the information on size as the sole criterion for screening for those dossiers that refer to nanomaterials/nanoforms. The use of “nano” by a registrant was considered to be an indication that the dossier may include nanomaterials or nanoforms within the scope of the registered substance and led to further analysis of the dossier.

Strengths and weaknesses of the screening strategy: An obvious weakness of the strategy is that where a registrant did not use the word “nano” to refer to a nanomaterial substance or nanoform of a substance included in the scope of the registered substance, such dossiers would not be found. However as registrants were encouraged to include information on nanomaterials and in particular to use “nano” as the pre-fix for any composition, analytical data, information requirement that referred to the nanoform as detailed in the technical

manual on how to include information on nanomaterials in IUCLID6, it is likely that where “nano” was not included in the dossier (1) the registrant did not consider or was not, in the absence of regulatory definition of nanomaterial, able to determine whether his substance was a nanomaterial/nanoform, (2) nanoforms were not within the scope of the registered substance or (3) the absence was due to the voluntary nature of the 'nano' information. Thus, the inclusion of “nano” in a nanomaterial relevant context in the dossier was assumed to be an indication that the registrant wished to explicitly address nanomaterials/nanoforms in the dossier.

5. SUMMARY OF THE OUTCOME OF THE SCREENING PROCESS

From the searches undertaken of the REACH registration database at the end of June 2011, it can be concluded that **78 substances** out of the ca. **4700 substances** on the REACH registration database included some information on nanomaterials in the dossiers.

From screening the ca. 3.2 million notifications in the C&L database at the end of June 2011, it can be concluded that 21 notifications had included some information on nanomaterials.

6. CONCLUSIONS

It should be noted that the screening employed does not find those substances that may include nanoforms if the key word “nano” was not included in any field of the respective registrations and notifications or in any file attached to the registrations. However, as registrants and notifiers were encouraged to use “nano” as the pre-fix for any composition, analytical data and information requirement that referred to the nanoform, we are confident that we have retrieved those substances where registrants/notifiers wished to explicitly include information on nanoforms.

From the searches undertaken, it can be concluded that **78 substances** out of the ca. **4700 substances** on the REACH registration database included some information on nanomaterials in the dossiers. Out of these 78 substances:

- **3 substances** could be considered to have included nanoforms within the scope of the registered substance: these registrations had nanomaterial selected as the form of the substance in the available picklists. Note however that there were 3 separate submissions for one of the picklist substances and only one of these submissions had nanomaterial selected as the form of the substance. The other two submissions included “nano” in the description of the substance where it was considered as a nanostructured material. The substances are listed in Annex 2.
- **2 substances** included possibly relevant information but a nanomaterial had not been selected as the form of the substance.
- **6 dossiers** included “nano” in the description of the substance but referred to the substance as being nano-structured rather than a nanomaterial.
- For the vast majority of substances listed based on the REACH registrations (**59 of the 78 substances listed**), “nano” was found solely in the context of read-across where there was no evidence that nanoforms are within the scope of the registered substance but extensive read-across from studies conducted on nanoforms of the

same or analogue substances were included in the dossier to fulfil specific REACH information requirements.

- A further **8 substances** also used extensive read-across from studies conducted on nanoforms of the substance or analogue substances but where it was explicitly stated that nanoforms were not within the scope of the registered substance.

From screening the C&L notification database, it can be concluded that **18 notifications** out of the ca. 3.2 million received included nanomaterial as the form of the notified substance. Free text searching of the name fields yielded an additional three notifications that had included “nano” in a relevant context in the chemical name field. One of the notifications where the picklist had been selected also included “nano” in both the chemical and EC name fields. It should be noted that for those substances that were registered by the REACH 2010 deadline, the C&L information is typically included in REACH registration dossiers and therefore a separate notification is not required. Thus, for a given substance, the parties that registered and notified are different. The substances retrieved are listed in Annex 3.

The list based on REACH registrations includes many of the substances on the OECD Working Party on Manufactured Nanomaterials (WPMN) list of representative nanomaterials (Cerium dioxide, aluminium oxide, iron oxide, zinc oxide, silica, titanium dioxide, silver, nanoclays, carbon black).³¹⁶ It should however be noted that some of the registrations explicitly exclude nanoforms from the scope of the registered substance but read-across from studies conducted on the nanoform to fulfil specific REACH information requirements. Others refer to studies conducted on nanoforms but do not explicitly state whether or not nanoforms are within the scope of the registered substance, while other stated that the substance was nanostructured rather than a nanomaterial.

It is also interesting to consider why certain substances were not found. An obvious reason that certain substances like fullerenes were not found from either database is that the tonnages manufactured and imported are below the tonnage triggers for the registration/notification deadlines and it is not classified as CMR, R50/53 or classified as hazardous under CLP. In some cases it may have been unclear to registrants and notifiers whether or not their substance should be regarded as a nanomaterial/nanoform. For example, although many inorganic pigments were registered by the 2010 deadline, very few pigments are included on the REACH registration based list. It is understood that inorganic pigments exist in grades that would have a fraction under the 100 nm cut-off that is widely used to discriminate between bulk and nanoforms. However, there is no consensus of what “particle” refers to in terms of the interpretation of the 100 nm cut-off. In addition, different methods for measuring particle size can yield vastly different values. Also there was no information available on how registrants should interpret the nano-status of substances that have particle size distributions with size fraction below 100 nm cut-off or whether the appropriate metric for reporting the particle size distribution should be mass or number based. However many of the substances on the C&L based list are pigments.

Annex 1: REACH requirements in terms of one registration per substance and the tonnage/hazard triggers that determine when a registration dossier shall be submitted.

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[http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono\(2010\)46&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2010)46&doclanguage=en)

Joint registration:

REACH applies to substances and all REACH registrants of the same substance are required to submit certain information jointly to the Agency (Art (11) of REACH). Other information is company specific and thus to be submitted for each registrant. From a technical perspective, this means that only one joint registration dossier is submitted for each substance. This joint registration dossier is split in a joint and individual (company specific) parts. This has implications on what information is retrievable from dossiers.

In a joint registration dossier, registrants of the same substance organise themselves such that a lead registrant submits certain information on behalf of all members of the joint registration (in the joint part of the registration dossier). Other – typically company specific – information is contained in the individual (registrant specific) parts of the joint registration. In some cases, registrants may also choose to submit information which would normally be submitted in the joint part in the individual part of their dossier, if these registrants have confidentiality or cost related concerns or disagree with the lead registrant on the selection of information.

The scope of the registered substance may thus be defined by the members of the joint registration to include or exclude particular forms or compositions of the substance registered. This may or may not be explicitly stated in the dossiers. Normally, the lead registrant submits all the required physico-chemical, eco-toxicological and toxicological information required by REACH for that substance. There is also a possibility to submit the joint chemical safety report (CSR) on behalf of all registrants. This information is required to be applicable to all forms/compositions of the substance registered by all members of joint registration. However, as explained above, there may be cases where this information is contained in the individual part of the dossier.

Thus, in terms of retrieving those dossiers from the database that include substance specific information on nanomaterials, registrant specific information on substance identity, manufacture, uses and exposure is reported in all dossiers received for that substance while physico-chemical, eco-toxicological and toxicological information is typically reported exclusively in the lead registrant dossier.

Tonnage triggers:

It is also important to note that although registrants of the same substance are required to submit jointly, they are only obliged to do according to the tonnages as manufactured/imported by their legal entity. For example, for a non-CMR, non-R50/53 substance, only those manufacturers/importers that are at or above the 1000 ton/yr trigger were required to register by the 2010 deadline. Manufacturers/importers with tonnages below 1000 tons/yr could also register by 2010 but are not required to do so. The registration deadlines for lower tonnages are 2013 (100-1000 tons/yr) and 2018 (1-10 tons/yr). Manufacturers/importers below 1 ton/yr do not have an obligation to submit a registration dossier for the substance. This has the direct implication that registrations received by the 2010 and thus stored in the ECHA database refer typically to those substances manufactured/imported ≥ 1000 tons per year per legal entity or those CMR substances that are at or above 1 ton/yr per legal entity or those R50/53 substances that are at or above 100 ton/yr per legal entity.

Annex 2: List of publicly available substances where information on nanomaterials was included in REACH registration dossiers received by the end of June 2011.

Note this list does not imply that the nanoform has been registered but solely reports the context in which nano-relevant information was included in the respective registration dossier received by ECHA for these substances. Only those substances that clearly included nanoforms within the scope of the substance are included.

Main context where nanomaterial relevant information was retrieved	EC / list number	Substance name	Section where "nano" indicated/found by free-text search			
			Nanomaterial selected as the "form of the substance"	"Nano" appears in public name/chemical name	composition name/composition description	Context where "nano" found in the phys-chem, eco-tox and tox IUCLID sections
registrant explicitly included nanoforms within the scope of the registered substance	207-439-9	calcium carbonate	2.1	chemical name and public name	both	Nano-composition
	215-150-4	cerium dioxide	2.1		both	Nano-composition
	215-609-9	Carbon Black	4.1			Read-across

Annex 3: Compiled public list of substances where information on nanomaterials was included in C&L notifications received by the end of June 2011.

Substance name	EC / list number	CAS number	Chemical name	Nanomaterial selected as the form of the substance	"nano" included in the chemical name	"nano" included in the EC name field of the notification
Manganese dioxide	215-202-6	1313-13-9		x		
Nickel monoxide	215-215-7	1313-99-1		x		
Zinc oxide	215-222-5	1314-13-2		x		

Substance name	EC / list number	CAS number	Chemical name	Nanomaterial selected as the form of the substance	"nano" included in the chemical name	"nano" included in the EC name field of the notification
Zirconium dioxide	215-227-2	1314-23-4		x		
Divanadium pentaoxide	215-239-8	1314-62-1		x		
Dicopper oxide	215-270-7	1317-39-1		x		
Anatase (TiO ₂)	215-280-1	1317-70-0		x		
Rutile (TiO ₂)	215-282-2	1317-80-2		x		
Carbon black	215-609-9	1333-86-4		x		
Aluminium oxide	215-691-6	1344-28-1		x		
Strontium titanium trioxide	235-044-1	12060-59-2	Strontium Titanate(SrTiO ₃)	x		
Titanium dioxide	236-675-5	13463-67-7		x		
Titanium nitride	247-117-5	25583-20-4		x		
617-568-6	617-568-6	844491-94-7	Silica, [[dimethyl[2-methyl-3-(methylamino)propyl]silyl]oxy]- and[(trimethylsilyl)oxy]-modified	x		

Appendix 4

List of effects and property improvements through nanotechnologies

Examples of the effects and property improvements through nanotechnologies³¹⁷

Functionality

Electronical/Electrical

- Conductivity
- Dielectric layers
- Superconductivity
- Thermoelectricity
- Electrochemical energy storage

Chemical

- Super-hydrophilicity
- Super-hydrophobicity
- Corrosion protection
- Catalysis
- Flame protection
- Fire protection
- Adsorption power
- Adhesion power
- Dissolving power

Thermal

- Heat protection
- Heat insulation
- Heat conduction
- Heat storage

Magnetic

- Magnetically soft materials
- Magnetoelectronics
- Magnetorheology
- Magnetic induction heat

Biological

- Antimicrobial effect
- Bioavailability
- Biocatalytics
- Moleculare recognition
- Biocompatibility
- Cell permeability

Application Examples

- Electrically conductive polymers through integration of carbon nanotubes into the polymer matrix for antistatic applications and electromagnetic shielding.
- Improved high-temperature superconductivity through nanoscaled substructures for increased ampacity and cost-efficient sol-gel-materials for layer production.
- More efficient thermoelectrics for power conversion of heat through nanostructured semiconductor connections.
- Nanoporous “low-k“-layers for the reduction of delay in conduction in CMOS-circuits
- Antifogging effect through super-hydrophilic titanium dioxide nanocoatings for glasses and exterior mirrors of cars.
- Dirt-repellent coatings, inter alia, through nanoparticle-modified fluor-siloxane/silane coating agents for textiles, furnishings and façade surface finishings.
- Fire-protection windows on the basis of transparent, nanoparticulate fire-protection gels and layers, which, under the impact of heat, form ultra-fine gas bubbles with strongly heat-insulating effect.
- Flame-inhibiting effect for plastic casings and cables through integration of catalytic nanoparticles in the polymer matrix, which prevent the spreading of flames by accelerated formation of non-combustible carbonization residues.
- Anti-fingerprint layers for stainless steel and metal surfaces on the basis of thin glass coatings
- Efficient adsorbent materials for gas storage or for the removal of contaminants through extended active surfaces and adjustable pore sizes
- Nanostructured heat-protection layers and alloys for turbine materials to achieve better energy conversion rates at increased working temperatures.
- Superinsulating nanofoams (aerogels, polymer foams) for heat insulation in buildings and industrial processes.
- Better heat conduction through nanofluids and nanocomposite materials on CNT-basis in industrial processes or in solarthermics
- Efficient heat storage through micro/nanoencapsulated phase change materials to be integrated in the facade components.
- Nanocrystalline, magnetically soft iron alloys capable of having extraordinary magnetic properties impressed on them, inter alia for high-capacity components in grids (e.g. toroidal tape core, transformers, choke coils).
- Magnetic layer stacks with giant magnetoresistance properties for magneto-electronic sensors and data memories.
- Dispersions of surface-stabilized nanoscaled iron particles (ferrofluids) with magnetically controllable viscosity for sealings, shock absorbers etc.
- Iron oxide nanoparticles for heat generation by means of alternating electro-magnetic fields (e.g. for switchable adhesives or hyperthermal cancer therapy).
- Antimicrobial equipment of plastics in medical engineering, furniture surfaces, textiles, through silver nanoparticles.
- Higher bioavailability of medical agents and dietary supplement substances through liposome encapsulation and nanoemulsions.³¹⁸
- Nanoparticles as carriers for the introduction of genetic material into cells (gene vectors) in gene therapy.
- Molecular recognition of diseased cells for effective drug delivery through surface functionalized drug-delivery systems.
- Nanostructured implant surfaces and nanoparticulate bone substitute materials for increased biocompatibility in regenerative medicine.
- Nanostructured templates and carrier substances for efficient biocatalysts.

³¹⁷ NanoDE-Report 2009- Status quo der Nanotechnologie in Deutschland (http://www.bmbf.de/pub/nanode_report_2009_en.pdf)

³¹⁸ Note that these are not necessarily covered by the Definition of Commission Recommendation 2011/696/EU.

Appendix 5

EU funded research in Nanosafety

The European Commission has started funding projects addressing specifically nanosafety since the 5th EU Framework Programme for Research and Technological Development (FP5, 1998-2002). Nanosafety is strategically addressed since the beginning of FP6, with a regular annual budget increase, from 800 k€ in 2004 to 30 M€ in 2010. Globally, from 2004 to 2010, FP6 and FP7 projects dedicated to nanosafety issues represented a total investment of 185 M€ (of which 130 M€ from the framework programme budget).

The framework programme calls are conceived to cover all aspects necessary for the risk assessment and risk management of nanomaterials: physico-chemical characterisations of nanomaterials, fate and behaviour in biological and environmental media, bio-nano interactions, nano-toxicity and nano-ecotoxicity, life cycle analysis of nanomaterial-embedded products (including recycling and final treatment), measurement devices, exposure, worker protection, risk assessment tools and risk management strategies.

These European projects are aimed at closing the knowledge gaps required for the assessment and development of relevant regulation founded on scientific knowledge. While the research is not aimed at producing regulatory assessment data for any specific nanomaterial currently in the market place, all projects have part of their activities that are specifically dedicated to dissemination of the project's results to stakeholders and general public. These activities include workshops such as the joint JRC/ENPRA stakeholders' workshops (www.enpra.eu), publications in peer-reviewed journals and public reports. A good example of a public report was produced by the FP7 ENRHES³¹⁹ project which performed a comprehensive and critical scientific review of the health and environmental safety of fullerenes, carbon nanotubes (CNTs), metal and metal oxide nanomaterials (<http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>). Participants to these European projects also often contribute to more regulatory oriented activities, such as the RIP-oNs studies and the OECD-WPMN work, or even sit in scientific committees such as SCENHIR, ensuring therefore that the knowledge produced in the projects be transmitted.

As an exception to the above, a topic addressing "Regulatory Testing" is planned for 2012 calls. The objective of the call is to provide legislators with a set of tools for risk assessment and decision making for the short to medium term, by gathering data and performing pilot risk assessment, including exposure monitoring and control, for a selected number of nanomaterials used in products. The outcomes of the project should also feed the work of the OECD-WPMN. A 10 M€ EC contribution is planned and a leverage effect from 3 to 5 times is expected from Member States and industries.

Finally, the EU NanoSafety Cluster is a DG RTD initiative to maximise the synergies between projects addressing all aspects of nanosafety including toxicology, ecotoxicology, exposure assessment, mechanisms of interaction, risk assessment and standardisation. The NanoSafety Cluster comprises 31 projects funded under FP7 and five projects funded under FP6. Additionally, national projects may contribute to the overall aims of the Cluster. The main objectives of the NanoSafety Cluster are: to facilitate the formation of a consensus on

³¹⁹ Engineered Nanoparticles - Review of Health and Environmental Safety (ENRHES), <http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report>.

nanotoxicology in Europe ; to provide a single voice for discussions with external bodies ; to avoid duplicating work and improve efficiency ; to improve the coherence of nanotoxicology studies and harmonize methods ; to provide a forum for discussion, problem solving and planning R&D activities in Europe ; and to provide industrial stakeholders and the general public with appropriate knowledge on the risks of nanoparticles and nanomaterials for human health and the environment. The NanoSafety Cluster also delivers yearly a compendium of all its projects, which includes consortia compositions, projects objectives and results. The last edition can be found at: www.nanosafetycluster.eu.

Appendix 6

Nanomaterials and worker protection: Main publications and websites

1. EU-OSHA³²⁰ REFERENCES TO NANOMATERIALS USE AT THE WORKPLACE:

- **Report - Expert forecast on emerging chemical risks related to occupational safety and health (2009)**

http://osha.europa.eu/en/publications/reports/TE3008390ENC_chemical_risks/view

EU-OSHA has published a series of expert forecasts providing an overview of the potential emerging risks in the world of work (physical, biological, psychosocial and chemical risks). Among the top ten emerging risks, three have in common their physico-chemical state as insoluble particles or fibres: nanoparticles and ultrafine particles, diesel exhaust, and man-made mineral fibres. The experts agreed that nanoparticles and ultrafine particles pose the strongest emerging risk.

- **Literature review - Workplace exposure to nanoparticles (2009)**

http://osha.europa.eu/en/publications/literature_reviews/workplace_exposure_to_nanoparticles/view

This report focuses on the possible adverse health effects of workplace exposure to engineered nanomaterials and possible subsequent activities taken to manage the risk. In order to provide a broad overview, information from different sources such as scientific literature, policy documents, legislation and work programs were collected. Documents from the EU were given priority, although national and international activities have also been described. Studies published up to November 2008 have been considered in the report.

As the conclusion of this review, the following topics were identified as priorities for future actions and activities:

- identification of nanomaterials and description of exposure
- measurement of exposures to nanomaterials and efficacy of protective measures
- risk assessment of nanomaterials in line with the current statutory framework
- in vivo studies for assessment of the health effects of nanomaterials
- validation of the in vitro methods and methods of physico-chemical properties as methods to determine health effects
- training of workers and practical handling guidelines for activities involving nanomaterials in the workplace.

³²⁰ European Agency for Safety and Health at Work, <http://osha.europa.eu/en/front-page/view>.

- **Literature review – Risk perception and risk communication with regards to nanomaterials in the workplace (2012)**

http://osha.europa.eu/en/publications/literature_reviews/risk-perception-and-risk-communication-with-regard-to-nanomaterials-in-the-workplace/view

This review found that communication on nanomaterials is still poor, with a majority of Europeans not knowing what nanotechnology is. Even in workplaces where manufactured nanomaterials are found, the level of awareness is low. For example, 75% of workers and employers in construction are not aware they work with them.

There are some initiatives to communicate the risks of manufactured nanomaterials and how to manage these (though not always targeted at the workplace), for example by major producers, some trade unions, national dialogues within some Member States, and Europe-wide through the Communication Roadmap by the European Commission. But much more still needs to be done (preferably jointly by policymakers, the social partners, national occupational safety and health bodies, public health agencies, sectoral associations, etc.) as poor risk communication may generate confusion and lead to unjustified fears or to underestimation of the risks, with consequent inadequate risk prevention. Risk communication strategies need to help employers make informed decisions about their workplaces and put adequate prevention measures in place, and to empower individual workers to take personal control of their own situations in order to protect themselves adequately.

- **Database of company Good Practice on the management of risks from nanomaterials in the workplace**

http://osha.europa.eu/en/practical-solutions/case-studies/index_html/practical-solution?SearchableText=&is_search_expanded=True&getRemoteLanguage=en&keywords%3Alist=nanotechnology&nace%3Adefault=&multilingual_thesaurus%3Adefault=&submit=Search

EU-OSHA has developed an on-line database of company Good Practice examples of good workplace management of manufactured nanomaterials which covers a variety of industries, such as textile, construction and medical applications, in different EU Member States.

- A number of **useful links** are also available in the agency's "Useful links" section "dangerous substances and new technologies"

Further to these EU-OSHA publications and the sources referenced in the bibliography list of these reports, a number of publications and references with relevance to occupational health and safety and the priorities identified in EU-OSHA studies are listed below:

2. EU MEMBER STATES

AUSTRIA

- The **Austrian Nanotechnology Action Plan** (available in English at <http://www.umweltnet.at/filemanager/download/60006/>) identifies needs for action and formulates recommendations related to, among others, worker protection

- Institut für Technikfolgen-Abschätzung, ITA (Institute of Technology Assessment of the Austrian Academy of Sciences)
 - Nanotrust project <http://nanotrust.ac.at/nano.ita.en/index.html>
 - Nanotechnologies – **nanotextiles, voluntary agreements** in industry (2010) <http://osha.europa.eu/en/news/nanotechnologies-2013-nanotextiles-voluntary-agreements-in-industry>
 - Nanotechnologies - **Assessment of nanosilver products** (2010) <http://osha.europa.eu/en/news/nanotechnologies-assessment-of-nanosilver-products>
 - **Neurotoxicity** of nanoproducts <http://osha.europa.eu/en/news/nanotechnologies-neurotoxic-effects-of-nanomaterials>
- Austrian **Labour Inspectorate**: has a section on nanomaterials on its webpages, in German only: <http://www.arbeitsinspektion.gv.at/AI/Arbeitsstoffe/nano/default.htm>. Also includes the results of **case studies of companies** working with nanomaterials, performed in 2009: http://www.ppm.at/downloads/umgang_mit_nano_im_betrieb.pdf. The Austrian Labour Inspectorate is also currently working on **guidelines for the safe use of nanomaterials at the workplace**.

GERMANY

- German Government **Nano Initiative Action plan** - also includes worker protection. Action Plan 2015 only in German; Action Plan 2010 also in English, available at: <http://www.bmbf.de/de/nanotechnologie.php>
- **Bundesanstalt für Arbeitsschutz und Arbeitsmedizin**, BAuA (German national institute for occupational safety and health):
 - Literature overview 2008-2010 related to the **use of nanotechnologies and occupational safety and health**, in German: http://www.baua.de/de/Bibliothek/Informationsdienste/Nanotechnologie.pdf?_blob=publicationFile&v=3
 - BAuA also provides a dedicated webpage with national actions, research and codes of practice, as well as information on the use of nanotechnologies and exposures to nanoparticles in practice. A selection of documents is translated into English. See http://www.baua.de/cln_137/de/Themen-von-A-Z/Gefahrstoffe/Nanotechnologie/Nanotechnologie.html for the German version and http://www.baua.de/cln_137/en/Topics-from-A-to-Z/Hazardous-Substances/Nanotechnology/Nanotechnology.html for the English version.
 - Among others, BAuA funded a project aiming at developing a **portable device to measure airborne nanoparticles in the workplace** (performed by IUTA, Duisburg – ended 2010). BAuA has now started to perform **workplace measurements of airborne nanoparticles in the industry**: (in German)

http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/Nanotechnologie/pdf/Forschung-Entwicklung.pdf?_blob=publicationFile&v=7

- Elaborated by BAuA and the Association of chemical industries (Verband der Chemischen Industrie, VCI): “**Guidance for handling and use of nanomaterials in the workplace**” (2007): <http://www.baua.de/cae/servlet/contentblob/717966/publicationFile/48357/guidance.pdf>
- Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, IFA (Institute for Occupational Safety and Health of the German Social Accident Insurance): Webpages on nanomaterials and OSH, including information on workplace measurement, risk assessment and prevention measures, in English (<http://www.dguv.de/ifa/en/fac/nanopartikel/index.jsp>) and in German (<http://www.dguv.de/ifa/de/fac/nanopartikel/schutzmassnahmen/index.jsp>)
- Berufsgenossenschaften der Bauwirtschaft, BG-Bau (German statutory insurance for the construction sector):
 - **Product list of nano-containing construction and cleaning products:** <http://osha.europa.eu/en/news/DE-nanoparticles-construction-cleaning>
 - The list was up-dated list in 2011: <http://www.bgbau.de/d/pages/praev/fachinformationen/gefahrstoffe/nano/PDF-files/nano-liste.pdf>
- Hessisches Ministerium für Wirtschaft, Verkehr und Landesentwicklung (Hessen Ministry of Economy, Transport and Development): **Guidance on the safe use of nanomaterials in the varnish and paint industry** (2009) in German only: http://www.hessen-nanotech.de/mm/Betriebsleitfaden_NanoFarbeLacke_Vorab.pdf
- Roller, M (Advisory Office for Risk Assessment, Dortmund) “**Carcinogenicity of inhaled nanoparticles**”, Inhalation Toxicology, 2009; 21(S1): 144–157

FRANCE

- French Ministry of Labour: **Plan Santé au Travail 2010-2014** (Plan for health at work): http://www.travailler-mieux.gouv.fr/IMG/pdf/PST_2010-2014.pdf

Sets up objectives with regards to nanomaterials and worker protection:

- Develop health surveillance of workers exposed to nanomaterials
- Strengthen the efforts to identify workplace exposure scenarios and characterise exposure in order to develop adequate measurement tools and methods
- Support EU level initiatives to implement legislative measures on traceability of nanoparticles
- Improve information to workers likely to be exposed to nanomaterial containing waste.
- Called on the French National Agency for Food, Environment and Occupational Health and Safety ANSES to draft a Good Practice guide on nanomaterials in the workplace in 2010 building upon the 2008 report “Nanomaterials – Safety at work” (<http://www.afsset.fr/upload/bibliotheque/258113599692706655310496991596/afsset-nanomateriaux-2-avis-rapport-annexes-vdef.pdf>)
- Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement et du travail, ANSES (French National Agency for Food, Environment and Occupational Health and Safety): New specific **Control-Banding tool for nanomaterials** <http://osha.europa.eu/en/news/fr-new-specific-control-banding-tool-for-nanomaterials-developed-by-anses>
- French **national public debate** on the general options on the development and regulation of nanotechnologies « Débat public sur les options générales en matière de développement et de régulation des nanotechnologies » http://www.debatpublic-nano.org/debat/debat_public.html

NETHERLANDS

- The Stoffenmanager Nano ModuleNano (2011): Adaptation of the Dutch **occupational risk assessment tool for workplace dangerous substances (“Stoffenmanager”) to nanomaterials.** Available at: <http://nano.stoffenmanager.nl/Default.aspx>
- Delft University of Technology (TU Delft), in cooperation with the Lawrence Livermore National Laboratory (USA): Paik, S., Y. & Zalk, D. M., Swuste P., “Application of a Pilot **Control Banding Tool for Risk Level Assessment and Control of Nanoparticle Exposures**”, Ann. Occup. Hyg., Vol. 52, No. 6, pp. 419–428, 2008 <http://annhyg.oxfordjournals.org/content/52/6/419.full.pdf+html>

- TU Delft, “Nanosafety Guidelines. Recommendations for research activities with ‘free nanostructured matter’”, 2008: www.veiligheidskunde.nl/xu/document/cms/streambin.asp?requestid=43531312-6BA0-400D-B916-7562D0EEBDE3
- Social and Economic Council of the Netherlands (SER), “Nanoparticles in the Workplace: Health and Safety Precautions”. Advisory Report. Working Conditions Committee. 2009. www.ser.nl/en/publications/publications/2009/2009_01.aspx

SPAIN

- Instituto Nacional de Seguridad e Higiene en el Trabajo, INSHT (National Institute for Safety and Hygiene at Work): “**Risk level assessment of nanoparticle exposure by control banding**” in Spanish only: <http://www.insht.es/InshtWeb/Contenidos/Documentacion/FichasTecnicas/NTP/Ficheros/821a921/877w.pdf>
- Instituto Sindical de Trabajo, Ambiente y Salud, ISTAS (Trade Union Institute for Work, Environment and Health): Web pages on nanomaterials, with practical information on measurement, risk assessment and control measures, in Spanish only: <http://www.istas.net/web/index.asp?idpagina=3332>

UNITED KINGDOM

- Health and Safety Executive:
 - Websection on nanomaterials <http://www.hse.gov.uk/nanotechnology/index.htm?ebul=hsegen&cr=8/31-jan-11>
 - In particular, on **fire and explosion properties** of nanopowders (2010) <http://osha.europa.eu/en/news/uk-2013-new-hse2019s-report-on-fire-and-explosion-properties-of-nanopowders>
- British Standards Institute, BSI:
 - “Nanotechnologies – Part 2: **Guide to safe handling and disposal** of manufactured nanomaterials.”, 2007: <http://www.bsi-global.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/PD-6699-2/Download-PD6699-2-2007/>
 - “**Guidance on the labelling** of manufactured nanoparticles and products containing manufactured nanoparticles”, 2007: <http://www.bsigroup.com/upload/Standards%20%26%20Publications/Nanotechnologies/PAS130.pdf>
- Institute of Occupational Medicine (IOM): “Safenano”, an initiative designed to help industrial and academic communities to quantify and control the risks to their workforce, as well as to consumers and the environment. The website includes a publication database, and some guidance e.g. on workplace risk assessment. <http://www.safenano.org/Home.aspx>

3. OTHER COUNTRIES

SWITZERLAND

- State Secretariat for Economic Affairs SECO, “**Safety data sheet (SDS): Guidelines for synthetic nanomaterials**”, 2010: http://www.seco.admin.ch/dokumentation/publikation/00009/00027/04546/index.html?lang=en&utm_source=oshmail&utm_medium=email&utm_campaign=oshmail-104
- Swiss Accident Insurance Fund SUVA: “Nanoparticles in the workplace” (2009), in German only, includes information on health effects, workplace measurement, risk assessment and management: http://www.suva.ch/startseite-suva/praevention-suva/arbeit-suva/gefahren-filter-suva/gesundheitsgefahrdende-stoffe/gs-nanopartikel/nanopartikel-arbeitsplaetzen-suva/filter-detail-suva.htm?WT.mc_id=shortcut_nanopartikel
- Swiss Nano-Inventory: by the IST, Institute for Work and Health, supported by the Federal Office of Public Health (BAG), the Federal Office for the Environment (BAFU), the State Secretariat for Economic Affairs (SECO), the Swiss National Accident Insurance Fund, and the French Agency for Occupational and Environmental Health Safety (AFSSET): “Swiss Nano-Inventory – An assessment of the usage of nanoparticles in Swiss industry” (2008): <http://www.suva.ch/ist-nanoinventory.pdf>
- Federal Office of Public Health,” Precautionary Matrix for Synthetic Nanomaterials”, structured method to assess the "nanospecific precautionary need" of workers, consumers and the environment, for enterprises, revised on the basis of users' experience at the beginning of 2010. <http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en>
- Groso A, Petri-Fink A, Magrez A, Riediker M, Meyer T, (Occupational Safety and Health, School of Basic Sciences, Ecole Polytechnique Fédérale de Lausanne), “Management of nanomaterials safety in research environment”, Part Fibre Toxicol. 2010 Dec 10;7:40, <http://www.ncbi.nlm.nih.gov/pubmed/21143952>

USA: National Institute for Occupational Safety and Health, NIOSH:

- Webpages on nanotechnologies and OSH: <http://www.cdc.gov/niosh/topics/nanotech/default.html>
- Research on **health effect of breathing nanoparticles** (2010): <http://osha.europa.eu/en/news/niosh-research-on-health-effect-of-breathing-nanoparticles>
- Approaches to Safe Nanotechnology - Managing the Health and Safety Concerns Associated with Engineered Nanomaterials (2009): <http://www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf>

- Research and prevention recommendations directed at workplace risk assessment: - Schulte, PA, et al., “Issues in the development of epidemiologic studies of workers exposed to engineered nanoparticles” J Occup Environ Med. 2009 Mar;51(3):323-35.. <http://www.ncbi.nlm.nih.gov/pubmed/19225418>
- - Trout, DB, Schulte, PA., “Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials”. Toxicology. 2010 Mar 10;269(2-3):128-35

CANADA

- Institut de recherche Robert-Sauvé en santé et en sécurité du travail, IRSST : “Engineered Nanoparticles. Current Knowledge about OHS Risks and Prevention Measures”. Second Edition, 2010. <http://osha.europa.eu/en/news/CAN-Engineered-Nanoparticles>
- Environment Canada: Environment Canada issued a notice in early 2009, requiring companies producing nanomaterials to file federal reports on those materials describing their toxicity, volume produced, and other relevant and readily available data. This would be required for all materials produced in quantities greater than 1 kg. Canada also plans to launch a voluntary program much like the NMSPP in the United States. <http://www.ec.gc.ca/subsnouvelles-news/subs/default.asp?lang=En&n=D179F162-1> . Also: “Guide for the Safe Handling of Nanotechnology-based Products” - 2009 Version: <http://www.ec.gc.ca/Publications/default.asp?lang=En&xml=F5DE8BCC-B2B9-4BEB-BB6E-89628B233AE6>

AUSTRALIA

- Safe Work Australia: “Engineered nanomaterials: Evidence on the effectiveness of workplace controls to prevent exposure” (2009): <http://www.safeworkaustralia.gov.au/ABOUTSAFEWORKAUSTRALIA/WHATWEEDO/PUBLICATIONS/Pages/RR200911ENEvidenceOnEffectiveness.aspx>
- Work health and safety assessment tool for handling engineered nanomaterials – 2010, Safe Work Australia, <http://www.safeworkaustralia.gov.au/AboutSafeWorkAustralia/WhatWeDo/Publications/Pages/AT201008WorkHealthAndSafetyAssessmentTool.aspx>

4. SPECIFIC EU PROJECTS

- **Compendium of Projects in the European NanoSafety Cluster:** The projects appearing in this compendium are supported financially by the European Union and the Governments of the FP6 and FP7 Associated States. The Nanosafety cluster will be coordinated by the Finnish Institute for Occupational Health . 2011 edition: http://www.nanoimpactnet.eu/uploads/file/NanoSafetyCluster/Compendium_2011_web.pdf, 2010 edition ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/compendium-nanosafety-cluster2010_en.pdf

- **Nanodevice:** Novel Concepts, Methods, and Technologies for the Production of Portable, Easy-to-use Devices for the Measurement and Analysis of Airborne Engineered Nanoparticles in Workplace Air
<http://www.ttl.fi/partner/nanodevice/Pages/default.aspx>
- **NANOSH:** exposure and health effects of selected nano-sized particles relevant to the occupational environment: <http://www.ttl.fi/partner/nanosh/Sivut/default.aspx>
- **NANOATLAS** of selected engineered nanoparticles. The objective for the Nanoatlas is to present a representative series of selected nanomaterials including high volume nanomaterials in commercial applications. NANOATLAS can be used, e.g., for the detection and measurement of typical engineered nanoparticles in products, dusts and tissue samples.
http://www.ttl.fi/partner/nanosh/progress/Documents/nanosh_nanoatlas.pdf
- **NanoSafe:** Safe production and use of nanomaterials:
<http://www.nanosafe.org/scripts/home/publigen/content/templates/show.asp?L=EN&P=55&vTicker=alleza>
- **NANOGENOTOX:** Safety evaluation of manufactured nanomaterials by characterisation of their potential genotoxic hazard
<http://osha.europa.eu/en/news/eu-nanogenotox>
- **Nanocap:** acronym for “Nanotechnology Capacity Building NGOs”; Aim: to deepen the understanding of environmental, occupational health and safety risks and ethical aspects of nanotechnology, structure discussion between environmental NGOs, trade unions, academic researchers and other stakeholders. Health and Safety section: <http://www.nanocap.eu/Flex/Site/Page918c.html?SectionID=1785&Lang=UK> After 2009 the individual participants continued their nano-activities and communicated about this using their own channels (see Contact and partners).

5. INTERNATIONAL

- **OECD** nanotechnologies Website:
http://www.oecd.org/department/0,3355,en_2649_37015404_1_1_1_1_1,00.html,
incl. [OECD Database on Research into the Safety of Manufactured Nanomaterials](http://www.oecd.org/document/26/0,3343,en_2649_37015404_42464730_1_1_1_1_1,00.html)
(http://www.oecd.org/document/26/0,3343,en_2649_37015404_42464730_1_1_1_1_1,00.html) and [Sponsorship Programme for the Testing of Manufactured Nanomaterials](http://www.oecd.org/document/47/0,3746,en_2649_37015404_41197295_1_1_1_1_1,00.html)
(http://www.oecd.org/document/47/0,3746,en_2649_37015404_41197295_1_1_1_1_1,00.html)

Three **OECD** reports address workplace issues:

- “Comparison of Guidance on Selection of Skin Protective Equipment and Respirators for Use in the Workplace: Manufactured Nanomaterials”. Series on the Safety of Manufactured Nanomaterials Nr 12. ENV/JM/MoONO (2009)17.: www.oecd.org/dataoecd/15/56/43289781.pdf
- “Report of an OECD Workshop on Exposure Assessment and Exposure Mitigation: Manufactured Nanomaterials”. Series on the Safety of

Manufactured Nanomaterials Nr 13, ENV/JM/MONO(2009)18:
<https://www.oecd.org/dataoecd/15/25/43290538.pdf>

- "Emission Assessment for Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance". Series on the Safety of Manufactured Nanomaterials Nr 11, ENV/JM/MONO(2009)16,
<https://www.oecd.org/dataoecd/15/60/43289645.pdf>
- **GoodNanoGuide:** Collaboration platform with information on workplace risk assessment and management, including for specific sectors and types of nanomaterials. Sponsored by, among others, NIOSH, IRSST, International Council of Nanotechnology: <http://goodnanoguide.org/tiki-index.php?page=HomePage>
- Specific ISO standards:
 - ISO/TR 12885:2008 "Health and safety practices in occupational settings relevant to nanotechnologies" (published)
 - ISO/TR 13329 "Preparation of Material Safety Data Sheet (MSDS)" (in preparation)
 - ISO/TS 12901-1 "Guidance on safe handling and disposal of manufactured nanomaterials" (in preparation)
 - ISO/TS 12901-2 "Guidelines for occupational risk management applied to engineered nanomaterials based on a "control banding approach" (in preparation)
 - More on the ISO standards on nanotechnologies at http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_tc_browse.htm?cmmid=381983

6. OTHER STAKEHOLDERS' ACTIVITIES

- **Nordic Council of Ministers:** "Evaluation and control of occupational health risks from nanoparticles", 2007. Includes an overview of uses and manufacturing of nanoparticles in the Nordic Countries, a review of methods for exposure and control measures, occupational exposure scenarios and a review of the quality of Material Safety Data Sheets. Available at: http://www.norden.org/da/publikationer/publikationer/2007-581/at_download/publicationfile
- European Trade Union Confederation, ETUC:
 - adopted a second resolution on Nanosciences and Nanotechnologies <http://osha.europa.eu/en/news/eu-etuc-adopted-a-second-resolution-on-nanosciences-and-nanotechnologies>

- contributed to the definition of the term ‘nanomaterials’
<http://osha.europa.eu/en/news/eu-etuc-contribution-to-the-definition-of-the-term-2018nanomaterials2019>
- **European Federation of Building and Wood Workers (EFBWW) and European Construction Industry Federation (FIEC)** within the context of the European Social dialogue: “Nano-products in the European Construction Industry – State of the art 2009”, http://hesa.etui-rehs.org/uk/newsevents/files/Nano_Executive_%20summary.pdf

Appendix 7

The JRC Nanohub database

1. BACKGROUND AND SCOPE

The JRC NANOhub (<http://www.nanohub.eu>) is an internationally available database on nanomaterials with web-based access, hosted by the JRC. It has been developed on behalf of the JRC as a tool to address nano-safety and measurements of nanomaterials, supported by an international stakeholder network from academia, industry, Member States, ISO, CEN, OECD, and NGOs. The JRC NANOhub hosts, among others, data and studies from the OECD sponsorship programme on the testing of a representative set of nanomaterials, as well as test and measurement results on materials from the JRC Repository of Representative Nanomaterials.

It serves the needs to:

- (1) Host information on nanomaterials in a structured way
- (2) Manage large datasets and collect multiple study reports for similar nanomaterial endpoints
- (3) Minimise time delays for information search and exchange to further enhance co-operations within research projects

The JRC NANOhub database is set up to host datasets for specific materials (or substances). For each specific material, information is collected in chapters and sub-chapters (or “endpoints”). The JRC NANOhub data structure builds on IUCLID chapters and the OECD Harmonised Templates (OHT). These IUCLID sections have been expanded for nanomaterials-specific endpoints listed by the OECD WPMN (Working Party for Manufactured Nanomaterials) in the Guidance Manual of the sponsorship programme. Once the new nanomaterials sections included in NANOhub have been tested and finalised, they will be submitted to the OECD for harmonization and implementation in a future release of IUCLID. Following such a IUCLID update the JRC NANOhub will be able to be based on IUCLID itself (if needed with using a custom configuration) so that further developments of IUCLID and IUCLID plug-ins could be used directly.

JRC NANOhub provides features to address data quality, to create reports and dossiers, and to exchange data. It contains search functions and web-based access functionality and it provides collaborating parties with a frame for hosting and sharing data. This way it facilitates cooperation between international parties using the World Wide Web.

The extent to which data are collected in JRC NANOhub (i.e. the “identification, gathering and upload” of data) now depends on the use, collection and exchange of data by, user groups, and the scientific community. The data format of JRC NANOhub does not constitute a requirement to address all data fields, but it can be seen as comfortable guidance to which data could contribute to gain an adequate picture of a nanomaterial.

2. STRUCTURE

The present JRC NANOhub structure provides the frame for the collection of nanomaterial data. It has three activity levels:

- (1) The **collaboration** through a project. Each project and its collaborating parties use their own specific and independent JRC NANOhub installation, with web-based access. The individual JRC NANOhub installations are hosted by the JRC. Data exchange between different projects is an option.
- (2) The **material(s)** investigated within the collaboration. Data regarding one, several or many specific materials (substances) are collected and managed in the JRC NANOhub installations as agreed within a collaboration.
- (3) The **chapter – subchapter (endpoint / endpoint study)** structure allows entering and modifying data with regard to the specific material.

Users access a project-specific installation from the www.nanohub.eu website (Figure 1).



Figure 1: Structure of JRC NANOhub: projects hosted in February 2012

The main chapters of the JRC NANOhub data structure are shown in Figure 2.

- 0 Related Information
- 1 General information
- 2 Classification and Labelling
- 3 Manufacture, use and exposure
- 4 Physical and chemical properties
- 5 Environmental fate and pathways
- 6 Ecotoxicological information
- 7 Toxicological information
- 8 Analytical methods

- 9 Residues in food and feedingstuff
- 10 Effectiveness against target organisms
- 11 Guidance on safe use
- 12 Literature search
- 13 Assessment reports

Figure 2: Structure of JRC NANOhub: Chapters

Within these chapters, the templates for the properties (or endpoints) were expanded to include, in addition to OHTs, new templates for nanomaterials taking into account new physicochemical endpoints, such as aggregation/agglomeration, zeta potential or crystallite size, as well as in-vitro toxicological information. An example for this format is shown in Figure 3.

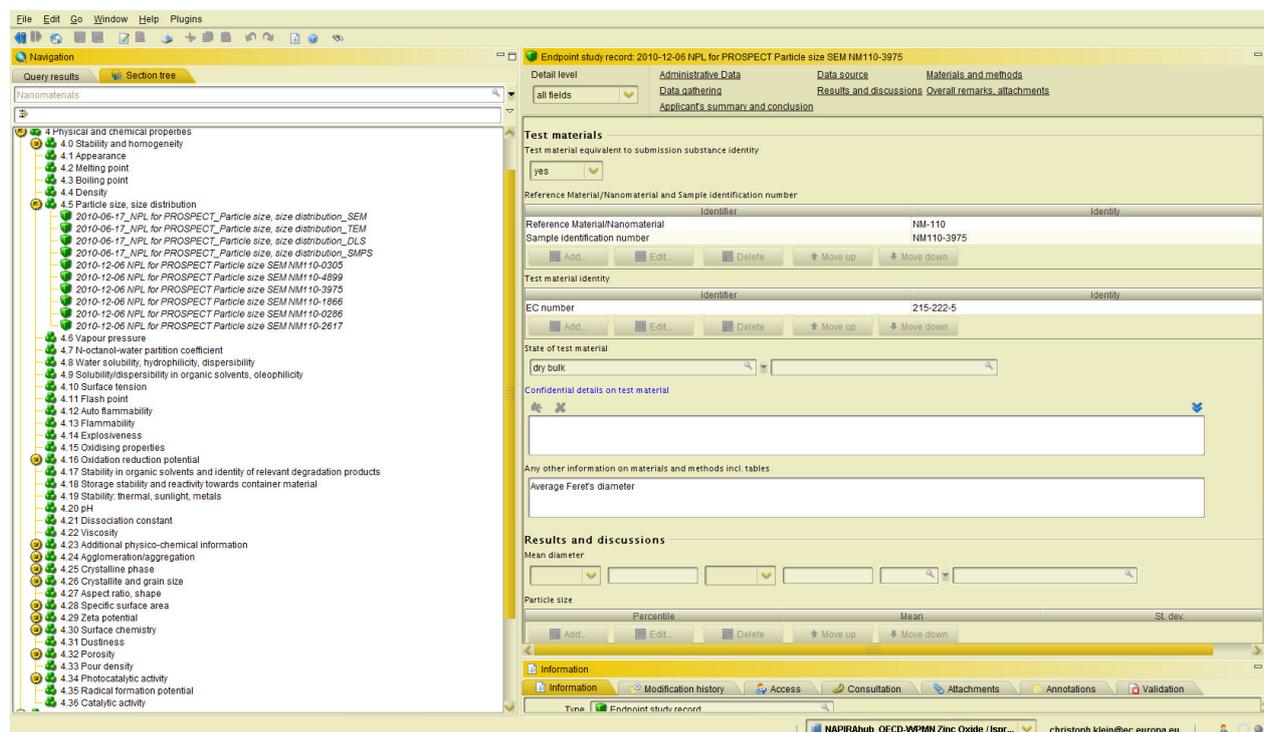


Figure 3: Chapter 4: Physicochemical properties and nanomaterial

3. FEATURES AND FUNCTIONS

As a IUCLID derivate, JRC NANOhub is designed **to store, maintain and exchange data coming from research projects**. This comprises features to:

- (1) Define materials (substances), endpoint study records
- (2) Enter, update and copy data (including copy-paste and use of clipboard)
- (3) Query and view data
- (4) Creation of dossiers for data exchange

JRC NANOhub also includes IUCLID features **on reporting and quality control**:

- (1) Reporting of comprehensive dossiers with selection options, e.g. regarding confidential information
- (2) Creation of dossiers
- (3) Quality control including track changes, data comparison, commenting, reliability scores

IUCLID features on **administration, user management and data sharing** are also available in JRC NANOhub:

- (1) Import, export functions
- (2) Filtering and data selection
- (3) Share data, dossier submission, compatible with other programmes (OECD, biocides)
- (4) User management and role management

4. PROJECTS HOSTED TODAY

A listing of hosted projects can be found on www.nanohub.eu.

In particular, the OECD WPMN uses the JRC NANOhub to collect data from its sponsorship programme on safety testing of a representative set of nanomaterials until a version of IUCLID is available where a range of nanomaterial specific endpoints has been implemented.

5. DATA CONTENT

Data obtained in the individual projects are hosted by JRC NANOhub. The data correspond to measurements and studies on materials from the OECD list of representative nanomaterials, from the European Repository of Representative Nanomaterials and other materials studied in the hosted projects.

Data quality of individual study entries is reported in the study dataset. This would comprise e.g. “reliable without restrictions” for a test study performed under Good Laboratory Practice. Data quality scores further support the identification of key studies and information, when large datasets would be merged and several study reports are collected for similar endpoints.

Several consortia have already decided to share all data; see www.nanohub.eu for an updated listing. Data today are entered by the individual parties that have generated the data or identified related information.

6. DATA OWNERSHIP, DATA ACCESS AND USER MANAGEMENT

The JRC provides the database installation and related service on request. It facilitates the installation and maintenance of the respective JRC NANOhub installation for a collaborating consortium. The consortium through its coordinator/representative fully decides about user access and use of content including sharing of information. User access is for example

managed by the JRC, and fully based on the validation of requests by the coordinator of a consortium.

Contractual agreements regarding the terms of use within collaboration are dealt with by the consortium. Ownership and confidentiality of the data or the willingness to share specific data can be declared and are provided for.

One free installation has been installed under ‘Open Science’, which provides any interested user with an area to explore the JRC NANOhub tools and features or to provide datasets to any other user or the scientific community. Access to this specific installation is granted to all registrants.

7. FURTHER STEPS

JRC envisages to further develop the JRC NANOhub application, following an upcoming requirements capture exercise with key stakeholders depending on the available resources and according to an agreed development plan. In such a development project JRC NANOhub will use as a basis the future IUCLID version including nanomaterial endpoints and be embedded in an overall project structure that will encompass not only the full datasets, but also a viewer (to reduce perceived complexity) and a wrapper portal providing additional functionality.

Appendix 8

Existing product databases on, or with relevance to, consumer products containing nanomaterials

1. REVIEW OF PRODUCT DATABASES

This review is an edited and shortened version of chapter 3 of the report "Development of an inventory for consumer products containing nanomaterials" prepared by RIVM by order and for the account of the Commission.³²¹

It includes also a short review of a product database ("nanowerk") not considered in the RIVM report.

This annex contains a review on inventories described in product databases and other databases linked to information on the use of nanotechnology and nanomaterials.

Generally, two types of databases dealing with nanomaterials/nanotechnology can be distinguished; 'product databases' and 'non-product databases'. Product databases can give answers to questions about products containing nanomaterials, while questions about specific information on, for instance, the use of nanotechnology and nanomaterials in general, not in specific products, may be answered by 'non-product' databases. Both types of databases were studied in this review.

2. EXISTING PRODUCT DATABASES

The following items were considered for each database:

- What is the target group of the database? Who is going to visit and use the database?
- What is the method of gathering and selecting products?
- Are criteria defined for the inclusion of products in the database?
- How are the products categorised?
- What additional information is given on the database?
- How is the database documented and presented?
- Are there specific countries to which the database is focused?
- Are there any costs of using the database?

These points will be discussed below for every database provided that the information is available.

The following existing product databases were investigated in the RIVM report:

³²¹ http://ec.europa.eu/environment/chemicals/nanotech/pdf/study_inventory.pdf

- (1) Woodrow Wilson database (“The Project on Emerging Nanotechnologies”)
- (2) ANEC-BEUC 2010 inventory of consumer products containing nanomaterials (ANEC-BEUC 2010)
- (3) Online database of German Environmental NGO ‘BUND’ (Friends of the Earth Germany)
- (4) The Mintel Global New Products Database (GNPD)
- (5) Household Products Database

Databases 1 to 3 are nano-specific product databases while 4 and 5 are more general product databases. Concerning the Household Products Database (5), however, it turned out that the database did not have a function to find products with a nanoclaim and will not be considered further here.

Below the first four product databases are described in more detail.

2.1. Woodrow Wilson database

The American Woodrow Wilson database was the first publicly available on-line inventory of nanotechnology-based consumer products. The inventory claims to be an important resource for consumers, policymakers, and others who are interested in learning about how nanotechnology is entering the market. Products have been selected for the Woodrow Wilson (WW) database by systematic web-based searches. These have ranged from exploratory searches, through searches on specific categories of goods, to following leads from multiple sources (including newspapers).

According to the database’s website, products within the database match the following criteria:

- They can be readily purchased by consumers;
- They are identified as ‘nano-based’ (term used but not explained by Woodrow Wilson) by the manufacturer *or* by another source;
- The nano-based claims for the product appear reasonable.

In every case, specific products from specific producers were identified.

Products are categorised in the following main categories and subcategories (between brackets):

- *Appliances* (heating, cooling and air; large kitchen appliances; laundry and clothing care)
- *Automotive* (exterior; maintenance and accessories)
- *Goods for Children* (basics; toys and games)
- *Electronics and Computers* (audio; cameras and film; computer hardware; display; mobile devices and communications; television; video)

- *Food and Beverage* (cooking; food; storage; supplements)
- *Health and Fitness* (clothing; cosmetics; filtration; personal care; sporting goods; sunscreen)
- *Home and Garden* (cleaning; construction materials; home furnishings; luxury; paint)
- Cross-Cutting (coatings)

However, since nanotechnology has broad applications in a variety of fields, also a number of ‘generic’ products are included in the database that are found in many places on the market or produced by many manufacturers, such as computer processor chips.

In addition, one company may offer several similar nanotechnology-based products and product lines. To avoid redundancy, for each company just a few samples were included in the WW database. This means that the database is not describing every product in a product line but that it provides an initial baseline for understanding how nanotechnology is being commercialized.

The information included for the products listed in the inventory is the following: information on the manufacturer, country of origin, product category, claims supporting the application of nanotechnology, and the date at which the entry was last updated. Hyperlinks to the manufacturer’s website are also provided.

No attempts were made to verify the nanoclaims of the products. This means that there may be false positives in the inventory (products of which producers claim that they contain nanomaterials, but which do not). Furthermore, products that clearly do not use nanotechnology have been avoided in this database, but some products have slipped through. For instance, GreenPan cooking utensils were mistakenly reported to have been manufactured using nanotechnology. This product has been removed from the database in September 2010. Additions to the inventory have been made periodically, as new information is received. Since the start of the project in 2005, the inventory has been updated six times. In the most recent update of 10 March 2011, 303 new products have been added since the latest update of August 2009. In the Consumer Products Inventory there are currently 1317 products, produced by 587 companies, located in 30 countries (as of 28 July 2011).

For some products, their availability could no longer be ascertained; to indicate this they were marked ‘Archive’. At the time these products were added to the inventory ‘live’ links were included. However, since then the company may have discontinued the product, gone out of business, removed a self-identifying ‘nano’ claim or simply changed their web address. In these instances a cached version of the product website was located using The Internet Archive with a date when the last update has taken place.

The database is presented on the website: <http://www.nanotechproject.org/inventories/consumer/>. Although the origin of the database is American, it is applicable for global use. Visiting the website is free of charge.

2.2. ANEC/BEUC 2010 inventory

The ANEC/BEUC 2010 inventory is a European inventory of products, available to consumers, with a claim to contain nanomaterials. ANEC and BEUC are both European

consumers' organisations (ANEC: European Association for the Co-ordination of Consumer Representation in Standardisation, BEUC: Bureau Européen des Unions de Consommateurs). The target group of the inventory is in principle consumers but the website claims that 'it is also useful for citizens, policymakers, and others who are interested in learning about how nanotechnology is entering the market'. Products were obtained via internet searches and/or using the feedback of member organisations of ANEC and BEUC. These member organisations searched products in shops or at trade fairs, or found them when they tested them in their consumer tests and/or when they acted in response to requests received from consumers.

Products within the ANEC/BEUC database have to meet two criteria:

- They claim to contain nanomaterials;
- They are available to European consumers.

Several product categories are identified which are of relevance to consumers, which are based on the categories of the WW database. A detailed table with product categories is provided the following table.

Category	Sub-Category
Appliances	Kitchen Appliances
	Laundry/ Clothing Care
Automotive	Maintenance & Accessories
Cross Cutting	Coatings
	Others
Electronic & Computers	No subcategory
Food & Beverage	Supplements
	Others
Goods for Children	No subcategory
Health & Fitness	Clothing
	Personal Care
	Sporting Goods
Home and Garden	Cleaning
	Construction Materials
	Others

Additional information on this inventory is that ANEC/BEUC has been able to check claims in different languages since the member organisations are located in different European countries. The inventory has been made twice, in 2009 and in 2010. The update has been carried out in the same way as the initial inventory. The inventory is a Microsoft Excel table which is available via the BEUC website: www.beuc.org. The current inventory contains 475 products. Visiting and using the inventory is free of charge.

2.3. Online database of German Environmental NGO ‘BUND’

The product database of BUND (acronym for Der Bund für Umwelt und Naturschutz Deutschland) is focusing on consumer products claimed to contain nanomaterials in Germany. The target group of the website are ‘consumers and everyone else who is interested’. No clear information is given on the website on how the products are obtained and which selection criteria were used.

The used categorisation for consumer products is presented in the following table.

Category	Subcategory
Auto	Autopflege (<i>car maintenance</i>)
Automotive	Fahrzeugbestandteile (<i>car components</i>)
Elektronik und Computer	Computer Hardware
Electronics and Computers	Electronisches Zubehör und Pflegemittel für Elektronik (<i>equipment and maintenance</i>)
	Mobiltelefone (<i>mobile phones</i>)
Freizeit Leisure	Reiseutensilien, Tassen und Koffer (<i>travelequipment, bags and luggage</i>)
	Sonstige (<i>other</i>)
	Sportgeräte und Zubehör (sports equipment and accessories)
Gesundheit Health	Sonstige (<i>other</i>)
Haus und Garten, Tiere Home, Garden, (domestic) Animals	Baumaterialien (construction materials)
	Farben und Lacke (<i>paint</i>)
	Gärtnern und Landwirtschaft
	Haustierzubehör und-pflege (pets equipment and maintenance)
	Möbel (Furniture)

	Wasch-, Reinigungs- und Pflegemittel (<i>Cleaning and coating products</i>)
Haushaltsgeräte Appliances	Große Küchengeräte (Large kitchen appliances)
	Heizung, Kühlung, Lüftung (<i>Heating, Cooling and Air</i>)
	Kleingeräte (small appliances)
	Kochutensilien (<i>cooking utensils</i>)
	Sonstige (<i>other</i>)
Körperpflege Personal Care	Kosmetika (<i>cosmetics</i>)
	Körperpflegeartikel (personal care products)
Lebensmittel und Getränke Foods and Beverage	Kochutensilien (<i>cooking utensils</i>)
	Lebensmittelaufbewahrung (<i>food package</i>)
	Nahrungsergänzungsmittel (<i>food supplements</i>)
	Zusatzstoffe und Verarbeitungshilfen
Medizinische Anwendungen Medical Use	Medizinprodukte (<i>medical products</i>)
Produkte für Kinder Goods for Children	Spielzeug (<i>toys</i>)
Sonstige Other	Beschichtungen und Pflegemittel für mehrere Anwendungsbereiche (<i>coating for multiple purposes</i>)
Textilien und Schuhe Textile and Shoes	Bekleidung und Wäsche (<i>upholstery</i>)
	Textil- und Schuhpflege (Textile and shoe maintenance/ coating)

The BUND database contains about 200 products (March 2011), but it is mentioned that more products will follow shortly. BUND attempts to give an overview of products that are available in Germany, by giving a selection of products from different product categories. For further extension of the list, the cooperation of consumers is requested to bring up new products. Consumers (in Germany) are called to report all nanomaterial containing consumer products that are found in shops and that are missing in the database. The database is accessible on the website of BUND: <http://www.bund.net>. Using the database is free of charge.

2.4. Mintel Global New Products Database (GNPD)

The Global New Products Database (GNPD) of Mintel is a general global product database with manufacturers, agencies and suppliers as primary target groups. GNPD claims that over 20,000 new products are added every month, from 49 countries worldwide. Note that GNPD is not nano-specific, so it is not specifically focused on products with a nanoclaim. GNPD scans the product labels and stores this information in their database. As a consequence, products with a nanoclaim can be selected. No specific criteria are mentioned for products to be included in the database. Nevertheless the database only includes products that can be purchased in the supermarket. The GNPD is accessible via the following link: http://www.gnpd.com/sinatra/gnpd/frontpage/&s_item=home.

To get information from the GNPD a paid license is required.

A product database not considered in the report by RIVM is

The Nanotechnology Products database of "nanowerk"

Nanowerk.com is a nanotechnology and nanosciences portal developed and maintained by US-based Nanowerk LLC. Its Nanotechnology Products database provides an overview of how nanomaterials and nanostructuring applications are used today in industrial and commercial applications across industries.

The database is presented on the website: <http://www.nanowerk.com/products/products.php>
The origin of the database is American, but it is applicable for global use. The criteria for inclusion of products are not explicitly defined. Information is collected via web searches and by input from product manufacturers and consumers.

It uses the categorisation:

- Chemicals
- Commodities
- Construction
- Energy
- Environment
- Food
- Industrial

- Information and Communications Technology
- Medical
- Precision Engineering
- Textiles and Garments
- Transportation

The Nanotechnology Products database of *nanowerk* contains 177 products (July 2011), with information on the products provided by the product manufacturer, and includes links to the manufacturer's product web page.

The database is public and visiting it is free of charge.

3. THE REACH REGISTRATION DATABASE

REACH³²² is the European Union Regulation on chemicals and their safe use. It deals with the Registration, Evaluation, Authorisation and Restriction of Chemical substances. The Regulation entered into force on 1 June 2007.

The REACH Regulation places greater responsibility on industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database run by the European Chemicals Agency (ECHA) in Helsinki. The Agency acts as the central point in the REACH system and manages the REACH-IT database.

REACH is specific for substances and it is possible to indicate that the registered substance is a nanomaterial or includes nanoforms in REACH registrations (for example, there is a voluntary tick-box to identify the substance or form of a substance as a nanomaterial). This information is retrievable from the registration database.³²³ It is however not always easy to identify which information relates to the nanoform(s) and which information to the bulk form(s) of the substances. Also, the description of uses in REACH dossiers is rather generic, and therefore it is not possible to identify concrete applications from the REACH dossiers. A screening of the REACH registration dossiers and CLP notifications was performed to identify information about substances in the nanoform. Methodology and outcome of this work is reported in Appendix 3.

4. OTHER DATABASES LINKED TO THE USE OF NANOTECHNOLOGY

In addition to the product databases discussed above, below an overview is presented on databases not predominantly considering products, but containing information related to the potential toxicity or hazard of nanomaterials. Two of the databases mentioned in the current

³²² Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), OJ L 396, 30.12.2006, p. 1.

³²³ <http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>

section provide information on experimental data and the projects and/or organisations in which these data are obtained. Two other databases specifically focus on industry needs.

- (1) The OECD Database on Research into Safety of Manufactured Nanomaterials
- (2) JRC NanoHub
- (3) nanotech-data.com
- (4) nanoproducts.de

4.1. The OECD Database on Research into Safety of Manufactured Nanomaterials

The OECD Database on Research into Safety of Manufactured Nanomaterials is a publicly available database of the Organisation for Economic Co-operation and Development (OECD).

It is an inventory of safety research information on manufactured (engineered) nanomaterials. The database contains information relevant to research on the environmental, health, and safety aspects of nanomaterials. The information is and will be based on projects that are planned, underway or completed. The details on the data on nanomaterials gathered in these projects may not be available via this database before they are published in the scientific literature.

The OECD database has been developed as part of the OECD activities to promote international co-operation in addressing human health and environmental safety aspects of manufactured nanomaterials. It is also intended to be an inventory of information on research programmes to help other projects of the OECD Working Party on Manufactured Nanomaterials (WPMN). This help may consist of identifying relevant research projects or storing information derived from the projects of the WPMN (including the sponsorship programme on the testing of manufactured nanomaterials).

The following information is stored in distinct fields:

- Project Title; Start date; End date;
- Project Status (Current; planned; or completed);
- Country or organisation;
- Funding information (where available, on approximate total funding; approximate annual funding; and funding source);
- Project Summary; Project URL; Related web links;
- Investigator information: name, research affiliation, contact details;
- Categorisation by material name, relevance to the safety, research themes, test methods;
- Overall outcomes and outputs of the project.

The site is publicly and freely available via:
(<http://webnet.oecd.org/NanoMaterials/Pagelet/Front/Default.aspx>)

4.2. JRC NANOhub³²⁴

The JRC NANOhub is a comprehensive IT platform (<http://www.nanohub.eu>), dedicated to the management of safety/risk assessment information of nanomaterials (substances).

The information gathered in this database is obtained from different EU projects as well as various OECD WPMN activities (Sponsorship programme for testing of a set of representative nanomaterials). The database consists of physicochemical properties and toxicity data of various engineered nanomaterials. These data are not publicly available.

4.3. Nanotech-data.com

Nanotech-data.com is the Database of Nanotechnologies for Luxembourg and areas in Germany and Belgium (Luxembourg, Lorraine, Rhineland-Palatinate, Saarland, Wallonia). The aim of the database is to inform about existing products, patents, processes, demands, news and events in the field of nanotechnology and to stimulate the knowledge transfer between research, Small to Medium-sized Enterprises (SME's) and large companies. The target public of this website are SME's, firms, researchers, institutions and individuals. The website provides detailed information about existing products, methods and services, application of interactive internet tools, simple and efficient handling and it is free of charge. The site is publicly and freely available via http://www.nanodaten.de/site/page_de_garde.html.

4.4. Nanoproducts.de

The website nanoproducts.de is a freely accessible internet database that deals with the marketing of products containing nanomaterials and/or products produced with nanotechnology on the internet. According to the website 'it offers services to industry in the area of product and technology transfer'. In this database, more than 450 different nanotechnology products are presented. The product spectrum comprises the fields of process engineering, analytics, raw materials, materials and commercial products. The aim is to list all commercial and non-commercial nanotech products and technologies. The website <http://nanoproducts.de/> is publicly available; using it is free of charge.

³²⁴ For more details, see Appendix 7.

Appendix 9 Standardisation

Standardisation is a process of consensus building on topics of technical-commercial nature, but also on items of broader societal relevance, in order to improve and facilitate communication, trade, innovation and transfer of technology. One distinguishes 'documentary' or 'written' standards (see section 1.) from physical or material standards (see section 2.). Both written and physical standards play an important role in harmonising multiple aspects of society and our daily lives, increasingly also those aspects that are related to nanotechnology.

1. DOCUMENTARY STANDARD DEVELOPMENT ACTIVITIES

1.1. General overview of actors and activities in nanotechnology standardisation

The International Organization for Standardization (ISO) is the larger of the non-governmental standard development organisations (SDOs) and provides a global forum for the development of 'documentary' or 'written' standards (as opposed to physical or material standards; see 2.). In the field of nanotechnologies, the ISO Technical Committee 'Nanotechnologies' (ISO/TC 229) plays a central role. It was created to complement and coordinate the nano-relevant standardisation work already undertaken by other, older ISO TCs. Similar responsibilities are carried by IEC/TC 113 and CEN/TC 352 in their respective mother SDOs (IEC, the International Electrotechnical Commission, and CEN, the European Committee for Standardization). Another major player in the nanotechnology standardisation area is the Organisation for Economic Cooperation and Development (OECD), which has devoted two working parties to the topic (Working Party on Manufactured Nanomaterials, WPMN, and Working Party on Nanotechnology, WPN). There are also a number of international organisations involved in the measurement aspects of standardisation, such as CIPM, the international metrology organisation, or VAMAS (the Versailles project on Advanced Materials and Standards), active in pre-normative research.

To facilitate the coordination of the work of the different SDOs the Nanotechnologies Liaison Coordination Group (NLCG) was created in 2008. The NLCG is hosted by ISO/TC 229. Twice a year, representatives of the NLCG members³²⁵ discuss issues of common interest, in order to improve harmonisation (for example of terminology) and to avoid unnecessary duplication in a time where resources are limited and in an area where expectations from regulators and from the public are high. The agenda of the NLCG meetings is organised based on the periodic liaison reports submitted by the members.³²⁶

Over the last three years, since the publication of the previous EC Regulatory Review, a number of specific nanotechnology standards and reports have been released, especially, but not only, by ISO/TC 229.^{327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349}

³²⁵ November 2011: NLCG counts 37 members, including ISO, CEN, IEC, OECD committees and working parties, CIPM and VAMAS; the European Commission is represented through liaison officers from the EC Joint Research Centre (JRC)).

³²⁶ The 6-monthly liaison reports are publicly available on the ISO/TC 229 livelink website (<http://isotc.iso.org/livelink/livelink/open/tc229>).

³²⁷ ISO/TS 10798:2011 'Nanotechnologies – Characterization of single-wall carbon nanotubes using scanning electron microscopy and energy dispersive X-ray spectrometry analysis'.

Currently, the CEN/TC 352 activities are dominated by the European Commission standardisation mandate M461, which requires the development of standards on about 40 different nanotechnology subjects. Since most of these 40 topics correspond to a number of documents, the size of this M461 mandate is unprecedented. For each of these items at least one standardisation committee has already indicated its intention to contribute to the development of the required documents. This currently concerns 7 ISO TCs, 6 CEN TCs and 1 IEC TC. While a number of the listed items in the mandate are already under development, work on the majority of items has yet to start. For some items this will require substantial pre-normative research, with an as large as possible international collaboration, for example through organisations such as VAMAS, or through EU-funded research (via CEN and the standardisation mandate, or directly via the Research funding programmes). Coordination of the M461 work will be carried out by CEN/TC 352. CEN/TC 352 and ISO/TC 229 co-operate through the Vienna agreement. This agreement is an important tool for European standardisation efforts in the nanotechnology area because the jointly developed EN ISO standards reconcile the desire of the EU legislator to refer to EU-wide adopted standards, with the preference of major EU Member States to develop the standards at the most international standardisation level possible (i.e. at ISO level). Until February 2012, CEN/TC 352 has only

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- 328 EN ISO 10801:2010 'Nanotechnologies – Generation of metal nanoparticles for inhalation toxicity
testing using the evaporation/condensation method'.
329 EN ISO 10808:2010 'Nanotechnologies – Characterization of nanoparticles in inhalation exposure
chambers for inhalation toxicity testing'.
330 ISO/TS 10867:2010 'Nanotechnologies – Characterization of single-wall carbon nanotubes using near
infrared photoluminescence spectroscopy'.
331 ISO/TS 80004-1:2010 'Nanotechnologies – Vocabulary – Part 1: Core terms'.
332 CEN ISO/TS 27687: 2008 'Nanotechnologies – Terminology and definitions for nano-objects –
Nanoparticle, nanofibre and nanoplate'.
333 ISO/TS 80004-3:2010 'Nanotechnologies – Vocabulary – Part 3: Carbon nano-objects'.
334 ISO/TS 80004-7:2011 'Nanotechnologies – Vocabulary – Part 7: Diagnostics and therapeutics for
healthcare'.
335 EN ISO 29701: 2010 'Nanotechnologies – Endotoxin test on nanomaterial samples for in vitro systems
– Limulus ameobocyte lysate (LAL) test'.
336 ISO/TS 11251:2010 'Nanotechnologies – Characterization of volatile components in single-wall carbon
nanotube samples using evolved gas analysis/gas chromatograph-mass spectrometry'.
337 ISO/TR 12885: 2008 'Nanotechnologies – Health and safety practices in occupational settings relevant
to nanotechnologies'.
338 ISO/TR 13121:2011 'Nanotechnologies -- Nanomaterial risk evaluation'.
339 ISO/TR 12802:2010 'Nanotechnologies – Model taxonomic framework for use in developing
vocabularies – Core concepts'.
340 ISO/TR 11360: 2010 'Nanotechnologies – Methodology for the classification and categorization of
nanomaterials'.
341 ISO/TS 10868:2011 'Nanotechnologies -- Characterization of single-wall carbon nanotubes using
ultraviolet-visible-near infrared (UV-Vis-NIR) absorption spectroscopy'.
342 ISO/TS 80004-4:2011 'Nanotechnologies – Vocabulary – Part 4: Nanostructured materials'.
343 ISO/TS 11308:2011 'Nanotechnologies -- Characterization of single-wall carbon nanotubes using
thermogravimetric analysis'.
344 ISO/TS 11888:2011 'Nanotechnologies -- Characterization of multiwall carbon nanotubes --
Mesoscopic shape factors'.
345 ISO/TS 12805:2011 'Nanotechnologies -- Materials specifications -- Guidance on specifying nano-
objects'.
346 ISO/TS 13278:2011 'Nanotechnologies -- Determination of elemental impurities in samples of carbon
nanotubes using inductively coupled plasma mass spectrometry'.
347 ISO/TS 80004-5:2011 'Nanotechnologies -- Vocabulary -- Part 5: Nano/bio interface'.
348 IEC/PAS 62565-2-1 'Nanomanufacturing - Material specifications - Part 2-1: Single-wall carbon
nanotubes - Blank detail specification'.
349 IEC 62624 Test methods for measurement of electrical properties of carbon nanotubes.

released 4 documents, each co-developed with ISO/TC 229, under the Vienna Agreement, with ISO lead.

1.2. Standard terminology and nomenclature

ISO and IEC have a joint working group (JWG1) for work on terminology and nomenclature. CEN has explicitly chosen to not develop a nanotechnology terminology of its own, but to use its liaison status and the Vienna Agreement to co-develop the ISO terminology. A detailed analysis of the ISO/IEC/CEN terminology related to nanomaterials is given in Appendix 1. The core elements of a series of terminology documents (EN ISO/IEC 80004-x) have been released over the last three years. Document 1 in this series (ISO/IEC TS 80004-1, released in 2009)³⁵⁰ defines terms such as nanotechnology, nanoscience, nanoscale and nanomaterial.³⁵¹ The first terminology document published by ISO/TC 229, the EN ISO TS 27687 document,³⁵² with the definition of the terms nano-object and nanoparticle, is currently under revision and will be released after revision as the ISO TS 80004-2 document. ISO TS 80004-3 covers the carbon nanomaterials (such as carbon nanotubes)³⁵³ and ISO TS 80004-4 deals with nanostructured materials.³⁵⁴ ISO TS 80004-5 is a document defining terms for use in the field of nanobiotechnology,³⁵⁵ and a number of similar terminology documents, specific for a certain field of nanotechnology (manufacturing, medicine, etc.) are under development. Conveniently, the complete list of terms and definitions in these documents, and in all other ISO documents, can be consulted in the ISO Concepts Database (<http://cdb.iso.org>).

Complementary to the work on terminology is the work on nomenclature. ISO and IUPAC, the International Union for Pure and Applied Chemistry, have recently decided to join their forces on this subject, and to develop a nomenclature for nano-objects in IUPAC, with help of ISO/TC 229.

1.3. Standard measurement methods

Several technical committees (TCs), in particular ISO TC 24/SC 4 (Particle characterisation), ISO/TC 201 (Surface chemical analysis) and ISO/TC 202 (Microbeam analysis), have already in the past developed standardised methods for measurements at what is now called the nanoscale. Naturally, this work continues in these committees. ISO/TC 229 and IEC/TC 113 complement (but not replace) the work of other technical committees on measurement methods not yet covered by other technical committees, for example on the characterisation of carbon nanotubes^{356,357,358,359,360,361,362,363,364} or on the creation of reproducible nanoparticle aerosols for inhalation toxicity testing.^{365,366}

³⁵⁰ ISO TS 80004-1:2010 Nanotechnologies – Vocabulary – Part 1: Core terms.

³⁵¹ Some of these terms were used in the definition, for regulatory purposes, of the term nanomaterial by the EC.

³⁵² CEN ISO/TS 27687: 2008 'Nanotechnologies – Terminology and definitions for nano-objects – Nanoparticle, nanofibre and nanoplate'.

³⁵³ ISO/TS 80004-3:2010 'Nanotechnologies – Vocabulary – Part 3: Carbon nano-objects'.

³⁵⁴ ISO TS 80004-4:2011 Nanotechnologies – Vocabulary – Part 4: Nanostructured Materials.

³⁵⁵ ISO/TS 80004-5:2011 'Nanotechnologies -- Vocabulary -- Part 5: Nano/bio interface'.

³⁵⁶ ISO/TS 10798:2011 'Nanotechnologies – Characterization of single-wall carbon nanotubes using scanning electron microscopy and energy dispersive X-ray spectrometry analysis'.

³⁵⁷ ISO/TS 10867:2010 'Nanotechnologies – Characterization of single-wall carbon nanotubes using near infrared photoluminescence spectroscopy'.

³⁵⁸ ISO/TS 11251:2010 'Nanotechnologies – Characterization of volatile components in single-wall carbon nanotube samples using evolved gas analysis/gas chromatograph-mass spectrometry'.

The specific CEN output in this area is likely to increase due to the standardisation mandate M461. This mandate, given by the European Commission to the European SDOs (CEN, CENELEC and ETSI) is focused on the areas of measurement and testing tools for the characterisation of nanomaterials and their behaviour, and to assess exposure to nanomaterials, complementing work carried out in the framework of OECD-WPMN and in the context of the implementation of REACH and CLP Regulations. Examples of mandated items for standardisation are methods for the detection, identification and quantification of the nanomaterial content of 'matrix materials', which can be consumer products (food, cosmetics, etc.), but also environmental materials (soils, water, sludge, etc.). The development of a comprehensive set of reliable methods for the detection of minute amounts of nanomaterials in such matrices will require years of research. This work has started already in projects supported by previous and current EU Framework Programmes for Research (for example FP7 project NanoLyse).

A particular set of measurement-related deliverables of the OECD are the OECD Test Guidelines, which are used to underpin the OECD Mutual Acceptance of Data (MAD) policy. MAD has been developed to relieve some of the burden of testing and assessing chemicals, and requires laboratories to implement Good Laboratory Practice (GLP). A similar concept is used by the world metrology organisation (CIPM) which has developed the International System of Units (SI) and tools (such as the Mutual Recognition Arrangement, MRA) to make measurement results SI-traceable, and therefore globally comparable. The culture of measurement laboratory accreditation, in accordance with, for example, ISO/IEC 17025,³⁶⁷ is slowly spreading into the nano-analysis area.

1.4. Conclusions

An important part of the efforts of SDOs such as ISO, CEN, IEC and OECD, in the nanotechnology area, is aimed at describing and specifying nanomaterials. These efforts should allow to distinguish and categorise different types of nanomaterials, based on new nanomaterial-specific terminology and nomenclature, and to develop measurement methods that allow one to verify the properties that are characteristic for one nanomaterial category or another. This approach should further enable moving from the 'case-by-case' approach in the assessment and evaluation of nanomaterials, which is limited, laborious and slow dealing with a limited number of materials, to a category approach, where data obtained on one material can be rightfully judged to be relevant for another more or less similar material.

³⁵⁹ ISO/TS 10868:2011 'Nanotechnologies -- Characterization of single-wall carbon nanotubes using ultraviolet-visible-near infrared (UV-Vis-NIR) absorption spectroscopy'.

³⁶⁰ ISO/TS 11308:2011 'Nanotechnologies -- Characterization of single-wall carbon nanotubes using thermogravimetric analysis'.

³⁶¹ ISO/TS 11888:2011 'Nanotechnologies -- Characterization of multiwall carbon nanotubes -- Mesoscopic shape factors'.

³⁶² ISO/TS 13278:2011 'Nanotechnologies -- Determination of elemental impurities in samples of carbon nanotubes using inductively coupled plasma mass spectrometry'.

³⁶³ IEC/PAS 62565-2-1 'Nanomanufacturing - Material specifications - Part 2-1: Single-wall carbon nanotubes - Blank detail specification'.

³⁶⁴ IEC 62624 Test methods for measurement of electrical properties of carbon nanotubes.

³⁶⁵ EN ISO 10801:2010 'Nanotechnologies -- Generation of metal nanoparticles for inhalation toxicity testing using the evaporation/condensation method'.

³⁶⁶ EN ISO 10808:2010 'Nanotechnologies -- Characterization of nanoparticles in inhalation exposure chambers for inhalation toxicity testing'.

³⁶⁷ ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories.

2. REFERENCE MATERIALS AND REPRESENTATIVE TEST MATERIALS

In the field of measurement and testing, the aspect of quality assurance is valued more and more. Essential tools in the development and validation of reliable test methods and in the establishment of quality control of routine measurement processes are reference materials and representative test materials.

2.1. Reference materials

Reference materials are materials which are carefully analysed for one or more of their properties, and which carry the obtained information (typically assigned property values) in a way that it can be used in measurement processes. Performing measurements on CRMs, and comparing the measured values with the attributed traceable certified property values, is not the only way for a laboratory to prove its proficiency, but it is certainly the most time-effective method, provided the appropriate CRM is available. The possibility to provide such proof of proficiency is essential for laboratories that are required to produce measurement results that will be compared against, for example, regulatory limits.

In the last three years, the European Commission, via its Joint Research Centre, has contributed significantly to the development of an increasing number of *non-certified* nanoscale reference materials, which are needed for method development, control charts and interlaboratory studies. A particular success was the release of a first colloidal silica *certified* reference material (CRM). CRMs have certified property values, which are needed for method validation and proficiency testing. The ERM-FD100 colloidal silica has certified property values for several equivalent diameters of the constituent silica particles.³⁶⁸ Current reference material development is working on more complex nanoparticulate systems (bimodal, polydisperse), in line with the measurement needs imposed by the new EU nanomaterial definition. Another main RM producer active in the nano-field is NIST (USA), which has released reference materials consisting of Au-nanoparticles and of carbon nanotubes.

2.2. Representative test materials

The characterisation of a particular property for a reference material requires the availability of a validated test method to assess that property. In the field of nanotechnology, there are a large number of newly developed test methods that are still to be validated. Also the applicability of existing, validated test methods to nanomaterials is sometimes questioned. In this case, that is, in the absence of validated test methods, reliable property values cannot be assigned, and therefore reference materials cannot be produced. Nevertheless, the level of consensus about the applicability of certain test methods can be increased by carrying out experiments in different laboratories on a common set of test materials. In the OECD-WPMN sponsorship programme a number of materials has been selected based on their representativity for the commercially available (or expected to be available) nanomaterials. These materials are used in the international interlaboratory evaluation of existing OECD test guidelines, the so-called Sponsorship Programme (see section 5.4). The European Commission, via its JRC, has contributed to this programme by the development of a series (NM-xxx) of such nanomaterials. They are primarily intended for the participants in the

³⁶⁸ Certification of equivalent spherical diameters of silica nanoparticles in water, ERM-FD100, A. Braun, K. Franks, V. Kestens, G. Roebben, A. Lamberty, T. Linsinger, Report EUR 24620 EN, European Union, Luxembourg, ISBN 978-92-79-18676-9, 2011.

OECD-WPMN sponsorship programme, but samples can also be obtained by other researchers (http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanomaterials-repository).