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EUROPEAN REGULATION AFFECTING NANOMATERIALS - REVIEW OF LIMITATIONS AND FUTURE RECOMMENDATIONS

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□ After learning about the potential risks associated with various specific nanomaterials, concerns have been raised about adequacy of existing regulation in Europe and what should be done to address any potential regulatory gaps related to nanomaterials. Understanding the limitations of the current regulation in regard to nanomaterials is a starting point in a democratic and transparent process towards adapting existing laws and facilitating an informed discussion about which kind of regulatory options best address the identified limitations. In the following we will introduce key pieces of European legislation affecting nanomaterials, analyze their limitations, and provide a number of recommendations on how these can be overcome. We find that, although nanomaterials are in principle covered by the scope of many of the existing legislative frameworks, it is often unclear, if current regulations are actually applicable when it comes to specific nanomaterials and their diverse applications. Main limitations seem to be: that requirements to do safety evaluations are triggered by production volumes by tonnage not tailored to the nanoscale, the profound lack of (eco)toxicological data, and that thresholds values and occupational exposure limits cannot be established with existing methodologies.

Keywords: Nanomaterials, European legislation, REACH, cosmetics, pharmaceutical regulation, food laws, worker safety directives, waste directives

INTRODUCTION

After learning about the potential risks associated with various specific nanomaterials such as C60, long carbon nanotubes, and nanosilver, one of the first logical questions for many politicians, regulators, academics and members of the public has been whether existing regulation is adequate in the short and the long term and what should be and is being done to address any potential regulatory gaps related to nanotechnology and nanomaterials (RS and RAE 2004, Macoubrie 2005, Chaundry *et al.* 2006, Gavelin *et al.* 2007).

The Commission of the European Communities has adopted a so-called incremental approach which focuses on adapting existing laws to regulate nanotechnologies and amending them in order to deal with nanomaterials. Understanding the limitations of the current regulation in regard to nanomaterials is a starting point in a democratic and transparent process towards adapting existing laws and facilitating an

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informed discussion about which kind of regulatory options best address the identified limitations.

In this paper we provide an analysis of key pieces of European regulation affecting nanomaterials including REACH, cosmetics regulation, pharmaceutical regulation, the worker safety directives, the waste directives and we identify key limitations and provide recommendations on how these can be overcome.

REGISTRATION, EVALUATION AND AUTHORIZATION OF CHEMICALS (REACH)

One of the key pieces of European legislation affecting nanomaterials is Regulation (EC) No 1907/2006 of the European Parliament and of the Council of the European Union called Registration, Evaluation and Authorization of Chemicals (REACH). REACH went into force mid-2007 (EP and CEU 2006). In short, the REACH consists of four elements:

1. Registration—Data collection on chemical use and toxicity.
2. Evaluation—Examination by governments of the need for additional testing and regulation of chemicals.
3. Authorization of chemicals—Requirements for firms to seek permission to use chemicals of high concern; and
4. Restrictions or complete ban of certain chemicals that cannot be used safely.

Except for the evaluation and restrictions process under REACH, there is a general shift of the responsibility in the registration and authorization process of REACH onto manufacturers and importers to provide data and information (including downstream users of chemicals). The registration process will happen gradually and by 30 November, 2010 manufacturers and importers had to register substances produced or imported in more than 100 tonnes per year. The same applied for substances produced in more than a 100 tons that have been classified as very toxic to aquatic organisms and substances produced in more than 1 ton that have been classified under Cat 1 or 2 carcinogens, mutagens or reproductive toxicants. By 1 June 2013 producers or importers of substances in quantities of more than 100 tons have to register and by 1 June 2018, registration of substances produced in more than 10 tons has to be completed (EP and CEU 2006, art. 23).

Although a number of substances, e.g. nanosilver and various forms of carbon nanotubes, have been pre-registered as nanomaterials, REACH does not specifically mentioned nanomaterials (European Chemical Agency 2010). One of the limitations of REACH in regard to nanomaterials is related to whether a nano-equivalent of a substance with different physicochemical and (eco)toxicological properties from the bulk sub-

stance would be considered as the same or as another substance under REACH (Chaundry *et al.* 2006). REACH defines a substance as *"a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition."* (EP and CEU 2006, art. 3).

Whether nanomaterials are considered to be a equivalent or different to the bulk material will have a major impact on the requirements put on manufacturers prior to placing nanomaterials on the market. If a nanomaterial is considered to be a different substance, hazard information would have to be generated for the registration dossier if produced in more than 1 tons/year. On the other hand, if the nanomaterial is considered to be the same as a registered bulk material, the appropriateness of the hazard information data would be open to discussion (Chaundry *et al.* 2006). In 2008, the Commission of European Communities published a review of the applicability of REACH arguing that although there are no specific provisions in REACH referring to nanomaterials the definition of "a chemical substance" covers nanomaterials (Commission of European Communities 2008a).

The Commission further stated that: "*When an existing chemical substance, already placed on the market as bulk substance, is introduced on the market in a nanomaterial form (nanoform), the registration dossier will have to be updated to include specific properties of the nanoform of that substance. The additional information, including different classification and labelling of the nanoform and additional risk management measures, will need to be included in the registration dossier. The risk management measures and operational conditions will have to be communicated to the supply chain*" (Commission of European Communities 2008a, p. 4). It is, however, highly unclear how companies should do this. Companies are urged to use already existing guidelines. Both the Commission of the European Communities (2008a) as well as the its Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR 2007, 2009) and others have pointed out that current test guidelines that support REACH are based on conventional methodologies for assessing chemical risks and may not be appropriate for assessing risks associated with nanomaterials. This means that although manufacturers and importers might be required to provide a Chemical Safety Assessment (if they produce or import nanomaterials in volumes more than 10 tons) they cannot rely on the toxicological profile of the equivalent bulk material and they cannot use existing test and risk assessment guidelines since these might not provide any meaningful results or be practically applicable due to the limitations of conventional methods.

It has been reported that the Commission was unable to secure the endorsement of its view from the Competent Authorities for REACH and

Classification, Labeling and Packaging (known as CARACAL) (Chemical Watch 2009) and the European Commission has now launched a multi-stakeholder project on nanomaterials that intend to look into substance identification under REACH.

Until recently carbon and graphite were exempted from registration under REACH, however this exemption was redrawn to address concern raised about carbonaceous nanomaterials (Führ *et al.* 2007, C & EN 2008). Companies will now have to register these materials if produced in quantities above one ton per producer or manufacturer per year. If it is produced in quantities greater than 10 tons per year a Chemical Safety Assessment has to be undertaken and if it meets the criteria for classification as dangerous or a PBT (Persistent, Bioaccumulative and Toxic) or vPvB (very Persistent and very Bioaccumulative), the manufacturer is required to develop exposure scenarios and undertake risk characterisation(s). So far no nanomaterial has been classified as such. It should be noted that a Chemical Safety Assessment can also be required if a nanomaterial is selected for further evaluation by a Member State or by the European Chemicals Agency due to specific concerns; or if a substance is a CMR (Carcinogenic, Mutagenic, or toxic for Reproduction), PBT, vPvB, ED (Endocrine Disrupting), or substance of equivalent concern. Even despite the recent amendments to REACH withdrawing carbon and graphite from the list of exemptions, it is highly unclear whether this would involve any additional obligations from producers of C60 and carbon nanotubes as well as from producers or importers of the final products containing C60 and carbon nanotubes, given what is known and accessible information about production, product contents, and expected consumer exposure (Franco *et al.* 2007). Another issue raised by Franco *et al.* (2007) is whether the annual production should be measured including impurities. All carbon based nanomaterials contain some degree of impurities due to the manufacturing process, however, a substance with a different degree of purity and composition can be classified as the same substance, provided hazardous properties do not differ significantly. This means that for instance, raw soot, NanomBlack® and purified fullerenes from the production of C60 could all be classified as the same, provided that the hazardous properties do not differ significantly.

Although there is no tonnage related exemption under REACH for authorization, restriction or classification and labeling requirements, a second limitation of REACH is that "*Substances manufactured or imported in volumes of less than 1 tons/year do not need to be registered*" and hence producers or importers are not required to provide toxicological data and assess environmental exposure. As noted by Chaundry *et al.* (2006) and Franco *et al.* (2007) this threshold would hardly be reached for many nanoparticles. Chaundry *et al.* (2006) estimates that the majority of applications is likely to fall outside the scope of REACH on the basis of the low

tonnage currently used in gram to kilogram quantities. Furthermore, the usually low concentration of nanomaterials in the final article could potentially exclude some nanomaterials from the REACH legislation, since no registration is required when the concentrations of a substance in the final article is lower than 0.1% w/w. However, a general lack of access to information about product formulations and nanoparticles concentration hampers determination of concentrations of substances by weight (Franco *et al.* 2007).

REGULATION OF COSMETIC PRODUCTS

As the first major piece of legislation to be amended in Europe, the cosmetics legislation was adapted in 2009 in order to comprise nanomaterials (EP and CEU 2009, Bowman *et al.* 2009).

In the cosmetics regulation a nanomaterial is defined as "an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm". Acknowledging that there are various definitions of nanomaterials the European Parliament and the Council of the European Union (CEU) call for the Commission to adjust the definition in the cosmetics regulation to definitions subsequently agreed at international level (EP and CEU 2009, art, 2).

For cosmetics already on the market, the regulation requires that the manufacturers inform the European Commission about the presence of substances in the form and identity of nanomaterials, and the reasonably foreseeable exposure conditions (EP and CEU 2009, art. 14). The presence of nanomaterials in the products has to be clearly indicated in the list of ingredients by the name of the nanomaterials (e.g. TiO2, silver) followed by the word "nano" in brackets e.g. (TiO2 [nano], silver [nano]). This requirement does however not go into effect until 11 July 2013 (EP and CEU 2009, art. 19, 40).

For cosmetic products not yet placed on the market the Commission has to be notified six months prior to commercialization (EP and CEU 2009, art. 16). The notification should include among other: size, physical and chemical properties of the nanomaterial; quantitative estimates of amount of nanomaterial to be placed on the market per year; the toxicological profile and the safety data of the nanomaterial relating to the use of the specific category of cosmetic products and finally, the reasonably foreseeable exposure conditions. This pre-market notification, however, only requires if the cosmetic products has not already been placed on the market before 11 January 2013.

The cosmetic regulation underlines the overarching principle that any cosmetic product commercialized shall be safe for human health when used under normal or reasonably foreseeable conditions of use and

that it is the manufacturers responsibility to ensure that this is the case (EP and CEU 2009, art, 3, 4).

Prior to placing a cosmetic product on the market Article 10 of the regulation underlines that the manufacturers have to ensure that a safety assessment has been performed in accordance with Annex I, which outlines the requirements for product safety information and assessment. As a minimum, it should contain among other a description of the composition of the cosmetic product and the function of the ingredients, physical/chemical characteristics and stability of the cosmetic product, microbiological quality, normal and reasonably foreseeable use, exposure to the cosmetic product (site(s) of application, surface area(s) of application; amount applied; duration and frequency of use; etc.), toxicological profile of the substances and notification of undesirable effects and serious undesirable effects (EP and CEU 2009, annex 1).

In regard to the toxicological profile specifically, the profile has to be established for all relevant toxicological endpoint considering all significant toxicological routes of absorption as well as the systemic effects. A particular focus has to be on local toxicity evaluation (skin and eye irritation), skin sensitisation, and photo-induced toxicity in the case of UV absorption. A margin of safety (MoS) has to be calculated based on a no observed adverse effects level (NOAEL) (EP and CEU 2009, annex 1). The proposal from the EP and the Council specifies that particular consideration shall be given to any possible impacts on the toxicological profile due to particle sizes, including nanomaterials. Finally, the product safety assessment should entail a concluding statement on the safety of the cosmetic product based on scientific reasoning (EP and CEU 2009, annex 1).

The cosmetic regulation requires the Commission to request the Scientific Committee on Consumer Safety (SCCS) to give its opinion within six months on the safety of such nanomaterial if the Commission has concerns regarding the safety of a nanomaterial for use in the relevant categories of cosmetic products and on the reasonably foreseeable exposure conditions. If the SCCS finds that any necessary data is lacking, it is the responsibility of the manufacturers to provide such data within an explicitly stated reasonable time period. This time period is non-extendable and the SCCS shall deliver its final opinion within six months of submission of additional data. The request from the Commission as well as the opinion of the SCCS has to be made publicly available (EP and CEU 2009, art. 16).

Acknowledging that there is inadequate information at present on the risks associated with nanomaterials the cosmetics regulation requires the SCCS to provide guidance in cooperation with relevant bodies on test methodologies which take into account specific characteristics of nanomaterials (EP and CEU 2009, art. 16).

In regard to restrictions for certain substances, article 16 specifies a high level of protection of human health shall be ensured for every cosmetic product that contains nanomaterials (EP and CEU 2009, art. 16). Taking the SCCS opinion into consideration the Commission may add a substance to lists of substances prohibited in cosmetic products or which cosmetic products must not contain except subject to the restrictions laid down where there is a potential risk to human health, including insufficient data.

The regulation also specifies that the SCCS should give opinions where appropriate on the safety of nanomaterials in cosmetic products, but also underlines that in the case of urgency relating to CMRs, nanomaterials and potential risks to human health of a cosmetic product normal regulatory procedures do not have to be complied with (EP and CEU 2009, art. 16).

Finally, by 11 January 2014, the Commission has to make a publicly available catalogue of all nanomaterials used in cosmetic products placed on the market indicating the categories of cosmetic products and the reasonably foreseeable exposure conditions. Furthermore, the Commission is obliged to prepare an annual status report for the European Parliament and the Council outlining e.g. the present and future use of nanomaterials in cosmetic products, the number of notifications, and the progress made nano-specific safety assessment methods (EP and CEU 2009, art. 16).

PHARMACEUTICAL REGULATION

Well-described medicinal products containing nanoparticles in the form of liposomes, polymer protein conjugates, polymeric substances or suspensions have been given Marketing Authorizations within the EU under the existing regulatory framework e.g. Regulation 726/2004 on authorization and supervision of medicinal products for human and veterinary use, Directive 2001/83/EC on medicinal products for human use, Directive 93/42/EEC concerning medical devices, Directive 90/385/EEC relating to active implantable medical devices, and Directive 98/79/EC on in vitro diagnostic medical devices (EP and CEU 2004, Council of the European Communities 1990, 1993, 1998, 2001).

There is no specific mentioning of nanomedicine in the EU legislation on medicinal products and devices, tissue engineering and other advanced therapies. None of these regulations or directives was written with nanomedicinal applications in mind and although their scope covers nanomedicine they have been accused for being general and non-specific and fraught with concerns and difficulties when it comes to dealing with drugs more complex than traditional ones (Editorial 2007, D'Silva and Van Calster 2008). In general it seems to be believed that existing regulation cover medical products based on nanotechnology and that the

fairly extensive pre-market safety assessment ensures that the benefits outweigh any identified risks or the adverse side-effects, (EGE 2007, N&ET Working Group 2007).

However, concerns have been raised that risk assessment, safety and quality requirements for medicine have to be fulfilled by conformity to established quality systems and published product standards that may not be suitable designed to address various aspects relating to nanomedicine. According to the European Medicines Agency (2006a), this might be especially relevant when it comes to novel applications of nanotechnology such as nanostructure scaffolds for tissue replacement, nanostructures that allow transport across biological barriers, remote control of nanoprobes, integrated implantable sensory nanoelectronic systems and multifunctional chemical structures for drug delivery and targeting of disease. It is furthermore unclear whether novel nanomedicine is to be regulated as a medicinal product or as a medical device (EGE 2007). Currently the mechanism of action is key to decide whether a product should be regulated as one or the other, however, nanomedicinal products may exhibit a complex mechanism of action combining mechanical, chemical, pharmacological and immunological properties, and combining diagnostic and therapeutic functions. Hence many of these novel applications are likely to span regulatory boundaries between medicinal products and medical devices (EGE 2007, European Medicines Agency 2006a).

When applying a new marketing authorization an environmental risk assessment is required. Compared to the risk assessment procedure under REACH, this involves a rough calculation of the predicted environmental concentration for surface water. If the PEC is predicted to surpass 0.01 ppb actions have to taken as environmental concerns cannot be excluded (European Medicines Agency 2006b). The 0.01 ppb threshold is not science-based and cannot be interpreted as a safe concentration (European Medicines Agency 2006b). When it comes to nanomedicice a mass-based action level could furthermore be problematic as mass-based concentrations might not be the most relevant metrics to describe the environmental profile of nanomaterials (Zhang *et al.* 2007, Baun *et al.* 2008).

Establishing the ecotoxicity of nanoparticles currently holds a number of limitations and challenges (Stone *et al.* 2009) and many of these shortcomings to environmental risk assessment are valid for nanomedical products as well. For instance, in the EU guidelines for risk assessment of medical products the octanol-water coefficient is used as surrogate value for bioaccumulation data, but so far there is no strong evidence that this approach applies for nanomaterials (SCENIHR 2007, 2009, Handy *et al.* 2008, Baun *et al.* 2008).

NANOFOOD REGULATION

In the EU, food and food packaging are regulated by a number of directives and regulations such as EU Food Law Regulation and the EU Novel Foods Regulation (EP and CEU 2002). The EU Food Law Regulation requires all food to be safe, something which – as an overarching principle – applies to all foods and food packaging containing nanomaterials as well, but has been criticized for being too loose (FOE 2008). None of the existing EU regulations applicable to agriculture, food or food packaging currently consider or mention nanoscale products or materials. If a substance as already has been approved for use as food ingredients, additives or packaging in its bulk form, it can also be used in this nanoform since there is no regulatory trigger to require new safety assessment or labeling due to particle size (FOE 2008). The existing regulation regarding food additives is in the process of being updated in the EU. During this process the European Parliament's Committee on Environment, Public Health and Food Safety stated that it wanted separate limit values for nanotechnologies and that the permitted limits for an additive in nanoparticle form should not be the same as when it is in traditional form (Halliday 2007). The EU Novel Foods Regulation requires mandatory pre-market approval of all new ingredients and products. Recently, the European Commission adopted a proposal to revise the Novel Foods Regulation with a view to improving the access of new and innovative foods to the EU market (Commission of European Communities 2008b). In the revised regulation the definition of novel food includes foods modified by new production processes, such as nanotechnology and nanoscience, which might have an impact on the food itself. This proposal recently failed after co-decision procedure where both the Council of the European Union and the Parliament had to agree on the final text of the regulation. The main areas of disagreement between the Council of the European Union and the Parliament in regard to nanomaterials seem to be the scope of the regulation, the extend of the novel food definition should include "nanotechnology and nanoscience" as well as "engineered nanomaterials", whether or not labeling should be mandatory and whether or not to have pre-market safety testing of nanotechnology and nanomaterials in food and packaging (European Parliament 2010).

The lack of adequate information and lack of test methods for assessing the risks of nanomaterials was mentioned by both the Council and the Parliament in the first line of revisions suggested to the Novel food regulation (European Parliament 2010). At current the European Food Safety Authority (EFSA) has to evaluate whether or not a novel food and its use as an ingredient presents a danger to consumers or misleads them once the European Commission receives an application for authorization of a novel food. The regulation requires assessments by EFSA on the compo-

sition, nutritional value, metabolism, intended use and the level of microbiological and chemical contaminants. Studies on the toxicology, allergenicity and details of the manufacturing process may also be considered. However, the regulation makes no distinction in relation to particle size, and hence nanoparticles will not require new safety assessments if the substance has already been approved in bulk form. In 2009, EFSA published a scientific opinion on the potential risks arising from the use of nanotechnology in food, concluding that nanotechnology aspects shall be considered when risk assessment guidance documents in the food and feed area are reviewed. Furthermore, they do, among other, recommend that risk assessment of nanomaterials in the food and feed area should consider the specific properties of nanomaterials in addition to those common to the equivalent non-nanoforms (EFSA 2008). Recently, EFSA closed for public comments on a draft guidance on risk assessment concerning potential risks arising from applications of nanoscience and nanotechnologies to food and feed. This guidance holds practical advice on how to complete risk assessments of nanomaterials used in food and food products (EFSA 2011).

SAFETY AT WORKPLACE DIRECTIVES

Safety at workplace in Europe is regulated through the Framework Directive 89/391 on measures to encourage improvements in the safety and health of workers as well as Directive 98/24 on the risks associated with chemical substances (Council of the European Communities 1989, 1998). As in the case of REACH and the Pharmaceutical legislation in Europe, nanomaterials are not specifically mentioned in these directives. However, according to the Commission of the European Communities (2008a) they fully apply to nanomaterials and "*…employers, therefore, must carry out a risk assessment and, where a risk is identified, take measures to eliminate this risk.*" The establishment of Occupational Exposure Limits (OELs) for workers is a key element of the Safety at Workplace directives however these are typically based on a complete risk assessment procedure which is presently not possible for engineered nanoparticles. OELs are furthermore typically based on mass concentration, but the most optimal dose metrics is still undefined when it comes to nanoparticles. To enforce the OELs, methods and equipment to detect nanoparticles in the workplace are needed. At the moment such methods do not exist which hampers the effectualness of the OELs (Franco *et al.* 2007, Stone *et al.* 2009). Given the lack of OELs specific for nanoparticles, many manufacturers refer to OELs of the bulk material. For instance OELs for dusts of graphite or carbon black instead of C60 and carbon nanotubes. However, there is evidence in the literature that these OELs are not valid due to the fundamentally different properties displayed by nanoparticles (Lam *et al.* 2004, Poland *et al.* 2008).

Material Safety Data Sheets (MSDSs) are the key mean to pass information about risk and safety down the supply chain. Besides providing some basic information about the material, the MSDSs also provide workers and emergency personal with information about the risks, protective equipment and proper handling of a substance as well as the OEL. Given the problems with establishing appropriate OELs, problems associated with establishing OELs are reflected in many of the MSDSs made available by the producers of nanomaterials For instance, there are examples of MSDSs that list a number of exposure control measures if ''engineering controls do not ensure that the OEL is not exceeded'', while clearly stating that OEL cannot be established (Franco *et al.* 2007).

WASTE MANAGEMENT OF PRODUCTS CONTAINING NANOPARTICLES

In Europe waste is currently primarily regulated through Directive 2008/98/EC of the European Parliament and of the Council on waste (EP and CEU 2008) and Council Directive 1991/689 on the management of hazardous waste (Council of the European Communities 1991). None of these directives mention nanoparticles.

In some cases nano-waste fall under specifically pieces of regulation. For instance, if C60 is used in oil lubricants, then the used oil is specifically regulated by Council Directive 75/439/EEC on the disposal of waste oils. This directive require members states to take measures to ensure safe collection and disposal of waste oils as well a recycling to the extend possible (Council of the European Communities 1975). In general, however, the fate of a given nanoparticles will depend on the treatment of the nanoproducts when it becomes waste - typically it ends up in landfills or becomes incinerated. Next to nothing is known about the behavior of nanoparticles in either of these waste management options. Depending on degradation of the product in which the nanoparticles are incorporated as well as their mobility, release might be anticipated through landfill leachates. The thermal stability of the specific nanoparticles will determine their fate during and after products are incinerated. Studies of the fate and behavior of nanoparticles after incineration are very scarce, but there are indications that C60 molecules behave like graphite and will be combusted. Carbon nanotubes remain stable even at very high temperatures (Cataldo 2002). At the moment, lack of (eco)toxicological data hampers the assessment of whether nanoparticles and some forms of nano-waste meet the criteria of hazardousness as defined under the Council Directive 1991/689 on the management of hazardous waste (Council of the European Communities 1991). Should this be the case more severe obligations would apply such as limit and emission values for the content of hazardous substances in waste and requirements for carrying out different forms of recovery (Council of the European Communities 1991, Franco *et al.* 2007).

DISCUSSION

Identified limitations of current regulation of nanomaterials

Besides the fact that nanomaterials are not specifically mentioned in most of the EU legislation analyzed here, it seems as if nanomaterials are covered by the broad scope of the various pieces of legislation. The Cosmetic regulation and the Novel food regulation are the exceptions to this rule and it seems that nanomaterials will be included in one form or the other. The question is, however, whether nanomaterials are covered when it comes to the specific procedures and guidelines laid down by the various pieces of legislation. For REACH the main areas of concern seem to be that it is unclear when a nano-equivalent of a bulk substance should be registered under REACH, and that production thresholds for when (eco)toxicological information has to be submitted, are not currently met for many nanomaterials (although they might be in the near future). Furthermore, even though companies are urged to use already existing guidelines, both the Commission of European Communities (2008a) and its Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR 2007, 2009) as well as others (Hansen 2009, Stone *et al.* 2009) have pointed out that current test guidelines supporting REACH are based on conventional methodologies for assessing chemical risks and may not be appropriate for the assessment of risks associated with nanomaterials. Somewhat similar issues have been raised for pharmaceuticals where the concern is that current product standards may not be suitably designed to address various aspects relating to novel applications of nanotechnology in nanomedicine (Baun and Hansen 2009). Furthermore, if the estimated environmental concentration of medical products is below 0.01 ppb and "no other environmental concerns are apparent", no further actions are to be taken for the medical product in terms of environmental risk assessment. Such pre-defined action limits could potentially be problematic as the new properties are expected to affect the environmental profiles of nano-based products (Baun and Hansen 2009).

In our analysis we identified three kinds of potential limitations of the existing regulatory frameworks when it comes to nanomaterials. In the first category of limitations are related to the limitations of definitions of what qualifies as a "substance", "novel food", "hazardous waste", etc. In the second category falls requirements triggered by thresholds values not tailored to the nanoscale, but based on bulk material, see e.g. REACH. The third category of limitations are related to lack of metrological tools, (eco)toxicological data, occupational and environmental exposure limits as required by e.g. the pharmaceuticals regulation and the Safety at Workplace Directives.

These findings are in line with the outcome of other independent analysis of the current regulation of nanomaterials. In a horizontal scop-

ing study, Chaundry *et al.* (2006) assessed the gaps in environmental regulation in the UK and the EU, media by media and sector by sector focusing on current and future products and applications of nanomaterials. In total 16 different sectors were included among others coatings, construction, and cosmetics. Chaundry *et al.* (2006) found that potential regulatory gaps could materialize itself if a) a piece of legislation is intended to address the human health impacts but fails to address possible environmental impacts of nanomaterials or nanoproducts and b) a piece of legislation fails to address a specific aspect of particular a sector, application, product or substance due to various threshold-, volume- or tonnage related exemptions or limitations in technical or scientific knowledge. (Chaundry *et al.* 2006).

Our analysis of the applicability of the current regulation on nanomaterials also showed that (eco)toxicological data and risk assessments are often necessary to support current regulation. However, risk assessment holds a number of limitations as well, and the short and long term feasibility of risk assessment of nanomaterials can be discussed. Risk assessment is often said to consist of four elements i.e. hazard identification, dose-response assessment, exposure assessment, and risk characterization. Each of the four steps hold a number of limitations as well. It is currently impossible to systematically link reported nanoparticle properties to the observed effects for effective hazard identification and though toxicity has been reported on for a range of nanoparticles, further confirmation is needed before one can say that a hazard has been identified.

Several of the studies mentioned above have reported on dose-response relationships. This goes for, especially, *in vitro* studies on among other C60, single- and multiwalled carbon nanotubes, and various forms of nanometals. Normally, dose refers to 'dose by mass', however, based on the experiences gained in biological tests of nanoparticles, it has been suggested that biological activity of nanoparticles might not be mass-dependent, but dependent on physical and chemical properties not routinely considered in toxicity studies (Oberdörster *et al.* 2005b). For instance, Oberdörster (1996) and Oberdörster *et al.* (2007) and Stoeger *et al.* (2006, 2007) found that the surface area of the nanoparticles is a better descriptor of the toxicity of low-soluble, low toxicity particles, whereas Wittmaack (2007a, b) found that the particle number worked best as dose metrics. Warheit *et al.* (2007a, b) found that toxicity was related to the number of functional groups in the surface of nanoparticles. However, it is still an open question which properties determine or influence the inherent hazards of nanoparticles partly due to the general lack of characterization of the nanoparticles tested (Hansen *et al.* 2007). Hence for dose-response assessment, it is still unclear whether a no-effect threshold can be established, what the best hazard descriptor(s) of nanoparticles is, and which are the most relevant endpoints. There is a

serious lack of characterization of the nanoparticles tested, which makes it difficult to identify which key characteristics – or combinations of key characteristics – that determine the hazards documented in (eco)toxicological studies of nanoparticles (Hansen *et al.* 2007, Wittmaack 2007a). But perhaps properties not yet identified in the scientific literature may be relevant for the hazard identification of nanomaterials. Although the lack of characterization is troublesome, it is hardly surprising as nanotoxicology is a very young field of research stemming from ultra fine particle research (Oberdörster *et al.* 2005a). A true understanding of the hazardous properties that materials begin to exhibit at the nanoscale requires a level of interdisciplinary research that has not yet been reached. In order to conduct and interpret scientific studies on the hazardous properties of nanomaterials, strong interdisciplinary collaboration is needed between nanoscientists, (eco)toxicologists and physicists, chemists, and material engineers.

In regard to exposure assessment (i.e. the third element of risk assessment) several studies have tried to assess current and future consumer and environmental exposure for nanomaterials, but these should be seen as "proof of principle" rather than actual assessment of the exposure. Realistic exposure assessment is hampered by: paucity of knowledge, lack of access to information, by difficulties in monitoring nanomaterial exposure in the workplace and the environment, and by the fact that the biological and environmental pathways of nanomaterials are still largely unexplored. Risk characterization being at the end of the line, the sum or maybe even the power all of these limitations are conveyed to calculating risk quotients for nanomaterials.

The European Commission has commissioned an expert-/multi stakeholder investigation of whether nanospecific amendments are needed to the current technical guidelines on chemical safety assessment. This has to develop among other specific advice on:

1. How REACH information requirements on intrinsic properties of nanomaterials can be fulfilled.
2. The appropriateness of the relevant test methods for nanomaterials.
3. Possible specific testing strategies, if relevant.
4. Information needed for safety evaluation and risk management of nanomaterials (especially, information beyond the current information requirements under REACH).
5. How to do exposure assessment for nanomaterials, hazard and risk characterisation for nanomaterials (Safenano 2010a, b).

The latter will involve threshold/non-threshold considerations, analysis of existing evidence related to setting limit values for nanomaterials, identification of critical items for dose description (mass, number con-

centration, surface area, particle size(s) etc.), whether and how no-effect-levels for health and the environment could be established and finally development of recommendations on the feasibility of whether categorisation of nanomaterials (e.g. different types of carbon nanotubes) in the hazard assessment compatible with the exposure assessment parameters/metrics in order to prepare a meaningful risk characterization (Safenano 2010a, b).

Recommendations in regard to the "Incremental approach"

The Commission of the European Communities has adopted a so called incremental approach which focuses on adapting existing laws to regulate nanotechnologies and amending them in order to deal with nanomaterials. In order for the incremental approach to be successful a number of changes and revision are needed to the regulatory frameworks analyzed above. So far, the Commission has only found it appropriate to implement one amendment to the regulatory frameworks analyzed above, i.e. carbon losing its exemption status under REACH. However, the other limitations need to be addressed as well sooner rather than later for the incremental approach to be successful, especially in view of the current pace of development of nanomaterials and applications. It is recommended that all nanomaterials are treated as distinct substances under REACH and other pieces of legislation until it is clarified whether all or only a few of them display unique (eco)toxicological properties at the nanoscale. Lowering or changing the current 1 ton per annum threshold per producer or importer for engineered nanoparticles to different thresholds and units than mass is recommended (RS and RAE, 2004, European Commission, Health and Consumer Protection Directorate General 2004). This would lead to a separate registration of nanomaterials under REACH. Besides providing the traditional physico-chemical properties when registering a substance, producers and importers of nanomaterials should be obliged to provide additional information such as shape, crystal structure, surface- area, charge and chemistry paying respect to the specific properties of nanomaterials. The new European Chemical Agency should develop and provide guidance to primary manufacturers and down-stream users on safety assessment of nanomaterials and a semi-governmental institution should be established in order to help industry do nanomaterials' characterizations and to do (eco)toxicological testing.

Efforts are underway internationally to identify potential exposure scenarios at workplaces and establish standard guidelines for safe handling of nanomaterials at the workplace and laboratories as well as identification of protection measures and development of efficient metrology infrastructures (NIOSH 2006, 2009, Paik *et al.* 2008). All of these initiatives can and will help address the limitations identified in the Safety at

Workplace Directives. However, it is expected that the establishment of Occupational Exposure Levels based on risk assessments is somewhat into the future and hence it is recommended that occupational exposure of nanoparticles is limited as much as possible.

Specific environmental regulations (e.g. REACH, Directives on hazardous wastes, etc.) often use terms like ''toxic'' or ''persistent'' as triggering factors to set emission limits, prohibitions and other requirements. These regulations require consistent meaning of these terms which is currently not possible given the lack of (eco)toxicological data for most nanomaterials. Although work is underway in order to produce such (eco)toxicological data for nanoparticles, much of this work is only just getting started and has yet to provide univocal data on which "toxicity" and "persistency" can be established or ruled out (Stone *et al.* 2009).

Despite the many knowledge and regulatory gaps identified, one of the largest obstacles is the lack of access to key information along the life cycle of the products. Key information during production, extraction and refining, manufacturing, use and final disposal of the products is not available due to manufacturer's secrecies and nondisclosure policies. It is impossible to obtain information on specific production volumes, the number of product units, concentration of nano-materials/particles in final products, or mass flows of nanoparticles from the raw material to the final product. Furthermore quantitative and qualitative characterizations of by-products, such as fullerenic soot and carbon nanotube fibres, as well as their fate cannot be exhaustively described. Without such information, public authorities will have a hard time monitoring and evaluating the effectiveness of the incremental approach. Some claims of confidential business information seem unreasonable (Hansen and Rejeski, 2008), and providing wider access to at least some information seems to be an important step in facilitating the availability of information up-and-down the supply chain and to other interested parties. In the case of emerging technologies, including nanomaterials, at a minimum information made publicly available for regular substances under REACH should also be made available i.e.: name, classification and labeling, physicochemical data, including information on pathways and environmental fate, results of each toxicological and ecotoxicological study, any derived no-effect level or predicted no effect concentration, guidance on safe use, and, to the extend possible, analytical methods for detecting direct human exposures or discharge to the environment.

Implementation of these recommendations will only address some of the immediate concerns related to the application of the incremental approach to regulate current manufacturing and use of nanomaterials. However, they fail to address other concerns, especially the ones related to nanomaterial yet to be developed, i.e. the third and fourth generation of nanotechnological development. More work is needed to cave out

what the impact of future generations of nanotechnology will be on European legislation.

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