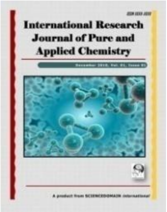

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Nanomaterials Life Cycle Analysis: Health and Safety Practices, Standards and Regulations – Past, Present and Future Perspective

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

A new technology always raises new issues with its introduction on the market. Nanotechnology is not an exception. The advantages of nanomaterials use are not to demonstrate anymore and so, the commercialization of consumer products based on nanotechnology doesn't stop increasing. The introduction on the market of nanoproducts also involves some uncertainties. Risks regarding the environment and human health are not well known by the scientist, and the legislation doesn't cover health and safety aspects related to nanomaterials. Especially, fate of nanoparticles during the life-cycle of nanoproducts is not fully experienced due the large variety of nanomaterials existing and their diverse applications.

It is safe to say that, given the explosive R&D and commercial uptake of nanomaterials unsurprisingly, the regulations governing the use and disposal of nanomaterials during its life cycle is behind the curve. The wide acceptance of nanotechnology by the consumers depends on

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alleviating the perceived safety related concerns. This paper aims to review the state of the art about exposure to nano-sized particles during life-cycle of nanomaterials. Also, future challenges and necessary work to ensure the success of nanotechnologies will be reviewed in this paper.

Keywords: Nanosafety; nanomaterials; life-cycle analysis; health & safety; nanoparticles release.

1. INTRODUCTION

Nanomaterials are one of the most promising technologies of this century. They are defined as materials composed of several phases one of which has at least one dimension of less than 100 nanometers [1]. Usually, a nanomaterial is a matrix (like ceramic, metal or polymer) with an addition of nanofillers of varying shapes, like spheres, fibres, platelets, particles, or tubes, and of different chemical compositions.

The annual consumption of nanomaterials is estimated at 118,768 metric tons, which corresponds to over $800 million, for 2010 [2]. Clay nanocomposites represent more than 50% of this annual consumption, and carbon nanotubes composites 21% [2]. And according to the Project on Emerging Nanotechnologies (PEN) inventory, in October 2013, there were 1628 consumer products based on nanotechnology on market.

This craze for nanocomposites can be explained by the large improvements in properties of the composites, such as enhanced modulus [3–6], dimensional and thermal stability [7–9], higher heat-distortion temperature [4,5,10], improved scratch and mar resistance [11–13], corrosion resistance [11,14,15], electrical conductivity [14], [16,17] and flame retardancy [18–20]. Compared to the traditional reinforcement, the addition of nanofillers in polymer implies a minor increase in the cost but reduces the weight. Actually, it is known that an addition of only 5wt.% of inorganic nano-particles in polymers is enough for a considerable improvement of the material's behaviour and properties compare to 20wt.% for a micro filler [11,21–24]. These improvements can be explained by the fact that fillers in nano-size allow a high volume-to-surface ratio of the nanoparticles, and so an increase of the contact surface between matrix and fibre [25]. It also allows a low inter-particles distance compare to micro-size fillers and reduces stress concentrations around the fillers.

However, nanomaterials also involve the uncertainty of a new technology, and health and safety aspects need to be covered. In fact, during its life-cycle, a nanotechnology-based product can release nano-sized particles exposing workers (including researchers), consumers and environment to potential risks. The impact of these risks is not well known [26–29], and actual legislation and regulation over the world in relation to chemicals and environmental protection does not cover this type of materials [30,31].

It is safe to say that, given the explosive R&D and commercial uptake of nanomaterials (for example, the number of submissions per year to the Journal of Nanoparticle Research increased every year and reached 2149 in 2013 [32]), unsurprisingly, the regulations governing the use and disposal of nanomaterials during its life cycle is behind the curve. The wide acceptance of nanotechnology by the consumers depends on alleviating the perceived safety related concerns. Also, from an ethical point of view, it is important to know the safety impact of any product on the market. A commercial product has to be safe, either for the consumers 'health, for every worker in contact with the product or involved in its production, but also for the environment. This paper aims to review the state of the art about exposure to nano-sized particles during life-cycle of nanomaterials. In addition, future challenges and necessary work to ensure the success of nanotechnologies will be reviewed in this paper.

2. NANOSCALE PARTICLES TOXICITY

The risk to human health and environment due to the use of nanocomposites is not well known [26,33–41]. Some studies done on animals have raised concerns about the potential risk associated with the use of nanocomposites [42], [43]. Also, studies about human exposure have already proved that nanoparticles can be hazardous to human health [44,45]. For example, inhalation of Carbon Nanotubes (CNTs) can have harmful effects on health: They facilitate blood coagulation, granuloma formation or lungs' inflammation [46]. Ursini et al. [47] noticed damage of membrane cells, increase of apoptotic cells and damage of DNA for cells exposed to MWCNTs. Exposure was tested during 24h, and changes start to appear for a concentration of only 5µg/ml of MWCNTs. Nano-silver easily accumulates in kidneys or other tissues, especially on female subjects [48]. Engineered nanoparticles were also found to be harmful for the environment. ZnO nanoparticles are toxic for both aquatic and terrestrial species even at low quantity (1 mg/l is enough) [49] and TiO_2 nanoparticles are considered as a risk for the aquatic environment for a concentration superior to 1.0 mg/L, especially it increases the oxidative stress on abalone [50,51]. Also, in a study done by Seaton et al. [52], it was observed that the nanoparticles in gas phase can be harmful to the workers working in mines. On the other hand, many animal studies explain the usefulness of nanoparticles [53–55]. Especially, we can cite the work of Hazer et al. [55] on prevention of shunt catheter infection in rats. They found that silver nanoparticle coating on polypropylene-grafted polyethylene glycol ventricular catheters allow an highest efficiency of the ventricular catheter in preventing the catheter-related infection and reduce inflammatory reaction.

Parameters Defining Nano-Objects Toxicity

To evaluate the risk of nanomaterial use, two areas need to be determined and combined: The exposure and their hazard potential (i.e. toxicological properties) [56].

For bulk or micro materials, toxicological properties are defined in term of mass, i.e. the limits are defined by the quantity, in grams, that you are exposed to during a given time. On the contrary, for nanomaterials, toxicity is directly linked to their physio-chemical properties. It has been established that the following characteristics influence the toxicity levels of the nanomaterials [57,58]:

- **Size** [59]: As seen before, the reduction in particle size increase to surface-to-volume ratio, and so enhanced toxicity per mass unit, and therefore are more likely than bigger particles to penetrate deeper into lungs, internal organs or blood-brain barrier [43], and to cause inflammation and epithelial damage [60]. For example, TiO_2 nano-particles were found much harmful in term of pulmonary-inflammatory neutrophil response than fine TiO_2 [43].
- **Shape**: The shape influences, as the size, the surface-to-volume ratio, and so toxicity per mass unit.
- **Chemical composition**: Chemical properties of nanomaterials are of importance to determine their toxicology [61]. For example, it was proved that carbon black was more harmful, in terms of inflammation and epithelial damage, than TiO_2 nanoparticles [60].
- **Surface modification and charge**: An enhanced surface area was described as a possible cause of tissue inflammation [57], [62]. Surface modifications such as by functionalization of single-walled carbon nanotubes [63] or coating of iron oxide nanoparticles (SPION) [64] were used in order to reduce cytotoxicity of nanomaterials.
- **Solubility and persistence**: a low solubility or degradability of nanomaterials allow them to persist in biological systems for longer time, and so increase the exposure time of toxic substances [57].

Exposure to nanoparticles may happen in the following (three) ways: Inhalation, ingestion or dermal penetration [65,66]. The most likely to occur is through inhalation [67], but data related to monitoring exposure of nanomaterials during the life-cycle of nanomaterials is not available for most of the scenarios. Indeed, the number of scenarios to study is extremely wide. The different mechanical or chemical stress situations, such as drilling, cutting, ageing, or abrasion, to analyse crossed with the number of engineered nanomaterials/matrix combination existing lead to a considerable amount of work. Also, the behaviour of nanomaterials regarding to living systems is not fully understood [68].

3. THE IMPORTANCE OF LIFE CYCLE ANALYSIS

The ISO 14040:2006 standard defines the Life Cycle Assessment (LCA) as the compilation and evaluation of the inputs, outputs and the potential environmental impacts of a product system throughout its life cycle [69]. In other words, it is the analysis of the impacts of a product on its environment during the different stages of its life (from the acquisition or production of the raw materials, to its disposal as a waste or recycling).

Currently, studies evaluating the potential risk to human health and environment only consider pristine engineered nanoparticles, but it is known that during their life cycle, nanotechnology-based products will suffer from different mechanical stress situation and physical or chemical aging [34]. These different situations can lead to a release of nano-sized particles but also to changes of nanoparticle characterises [61,70]. So, the nano-particles released during the LCA can be very different, in terms of shape, chemical composition, or surface modification compared to the pristine engineered nanoparticles (ENP) integrated in the matrix [71], as shown in **Error! eference source not found.** [33] and it is essential to take into account the whole life cycle of a product in order to assess the relative environmental sustainability performance of nanoproducts [34,72,73].

Also, exposure is a key factor to assess the risk associated to nanomaterials [61]. Engineered Nanomaterials (ENMs) have various applications, and so interact in different ways with the environment. Koehler et al. [74] estimated that the amount of nanoparticles released from a nanoproduct depends on the amount of nanofillers in the product, the product's lifetime, the manufacturing process of the product and the use of it. So, for a good assessment of the exposure scenarios and health & safety risks, it is the life cycle of the nanoproducts containing nanomaterials which need to be studied [72]. The life cycle of nanoproducts can be described in 3 main stages: the production of nano objects, the manufacturing and machining of nanocomposites, the use by consumers, and the end of life (recycling or waste).

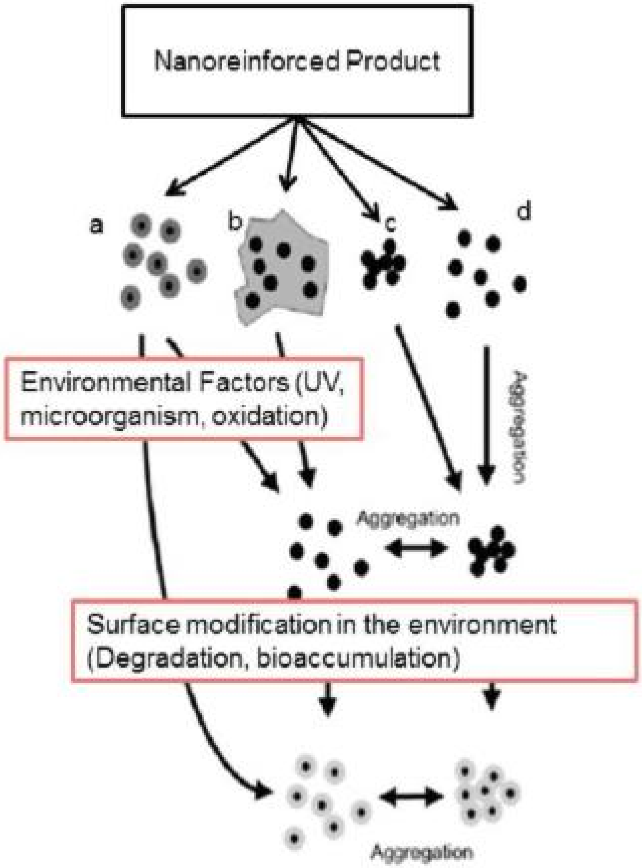

Fig. 1. Release of nanoparticles from products and (intended or unintended) applications: (a) release of free nanoparticles, (b) release of aggregates of nanoparticles, (c) release of nanoparticles embedded in a matrix and (d) release of functionalized nanoparticles. Environmental factors (e.g. light, microorganisms) results in formation of free nanoparticles that can undergo aggregation reactions. Moreover, surface modifications (e.g. coating with natural compounds) can affect the aggregation behaviour of the nanoparticles [33]

3.1 Manufacturing of Nanoobjects and Nanomaterials

Exposure measurement is necessary in order to assess acceptable exposure levels and so to implement correct Health & Safety regulations. Exposure studies and measurement of nanoparticles was carried out at companies or laboratories producing engineered nanomaterials [75–79]. An overview of the different studies found in the literature is presented Table 1. They can be classified in two different types: Real exposure measurement, carried out in industry, and laboratory experiment, aiming to reproduce an industrial process but with a considerable reduction of the background noise. The results of these studies indicated that workers were most likely to be exposed to free ENMs during the production and the handling of dry powders.

Also, release and exposure to nanoparticles is related to the mechanical or chemical process undergone by the material and the type of materials. Depending on the type of nanofillers, the production consist of milling and grinding of bulk material or starts from nucleation with particle growth by condensation and/or coagulation [56]. In the second option, the release of nano-sized particles is influenced by two parameters:

- production via the gas [80] or liquid phase [81];
- production in an open [82] or closed process [83,84].

In general, compared to other processes, production of nanomaterials via liquid phase process was the safer option as it was less likely that the nano materials would be inhaled during the processing. However, more work needs to be done to establish the relative ‘safety’ of the processes as Park et al. [81] found that nanoparticles and agglomerates were released in the air from the reactor during production of silver nanoparticles by liquid phase. Also, the number concentration of nanoparticles was higher than for nanoparticles release during handling of a dry powder of silver nanoparticles.

Production in an open process results in high concentration of airborne nanoparticles which are breathable by workers [82]. On the other hand, in the case of a close process, several studies found that enclosures are efficient and particle concentrations are insignificant outside it [75,80,84,85]. For example, it was shown [84] that the release of nanoparticles was negligible during production of Carbon Black in a reactor. The same study points to the fact that preventive maintenance is necessary in order to keep normal operating conditions. Indeed, after a leak in the pelletizing area, the number of nanoparticles was found to be around 10^6 particles/cm^3. Similar conclusions were drawn by Wang et al. [85] Who studied nanoparticle exposure in a Carbon Black manufacturing industry.

Also, several studies point the fact that ventilation and good enclosure are key factors in order to reduce the workers’ exposure to nanoparticles released during production [77,86,87]. For example, Han et al. [77] Found that an enclosure and exhaust ventilation could reduce the nanoparticles concentration from around 180 CNT/cm^3 to 0.05 CNT/cm^3 during blending of MWCNTs. Usage of a fume hood during synthesis of SWCNTs in a furnace by chemical vapour deposition was also demonstrated to efficiently remove the released nanoparticles. Indeed, the amount of nanoparticles was negligible (2000 particles/cm^3) outside the fume hood, at the breathing zone, compared to a concentration of 107 particles/cm^3 measured inside the fume hood, next to the source [87].

Production of engineered nanomaterials also generates waste. Characterisation of this waste is not available [72] and so the safe disposal process is also not defined. Breggin and Pendergrass [105] reported that the distinction between normal waste, hazardous waste, waste for incineration or for landfilling, in order to define these waste was not clear. However, some countries made significant progress in the last few years concerning this subject. The British Standard Institution, for example, published in 2012 a guide for “Disposal of manufacturing process waste containing nano-objects” [106]. This guide defined how to treat nano-object containing waste according to their phases (solid or liquid) and their characterization (hazardous or not, water soluble/insoluble). Also, behaviour regarding contaminated wipes, clothing, filters, etc., is defined. In United States, disposal and waste management of nanomaterials is regulated by a law named Resource Conservation and Recovery Act, subtitle C [107].

Table 1. Release scenarios concerning manufacturing and handling of nanoobjects/nanomaterials found in the literature

Nanoobjects	Activities	Used equipment	Ref.
Carbon Black	Reactor & Pelletizing	SMPS, APS & TEOM	[84]
Carbon Black, MWCNT, Fullerenes	Probe sonication	CPC	[88]
SWCNT	Handling	CPC & OPC	[86]
Fumed silica	Bag emptying	SMPS or ELPI & CPC	[89]
Carbon Black	Packaging, Warehouse & Pelletizing	MEAD, NSAM & SMPS	[85]
Silver	Liquid phase process & Handling	SMPS	[81]
CNT, CNF, fullerenes	Production (arc reaction, sweeping & vacuuming)	SMPS & CPC	[79]
Fullerenes	Production (bagging & agitation)	SMPS & OPC	[76]
SWCNT & MWCNT	Production (synthesis by Chemical Vapour Deposition)	FMPS & APS	[87]
CNF	Production, Mixing, Drying & Thermal treatment	CPC, ELPI & FPSS	[90]
Silicon nanoparticles	Production (Generation in reactor, collection, bagging, packaging & cleaning)	UNPA, FMPS, NSAM, CPC & SMPS	[80]
CNTs	Mixing with polymer, extrusion, water cooling & pelletizing	UNPA	[80]
CNTs	Production (by CVD) & Handling	FMPS & CPC	[75]
MeO	Production, handling, packaging & cleaning	CPC & SMPS	[82]
CNFs	Handling & Mixing of CNFs, Chopping & Cutting of CNF-based nanocomposites	CPC & ELPI	[78]
TiO2, SiO2, WO3, Cu/ZnO, Cu/SiO2	Production (Flame Spray Pyrolysis)	SMPS, CPC, DustTrakTM & SidePakTM	[91]
ZnO	Production (Mixing into water, handling & spraying)	SMPS & CPC	[92]
Lithium titanate metal oxide	Wet milling & spray drying	CPC & OPC	[93]
Nanofillers	Vapour Deposition Process (PECVD & PVD) & Polymers Extrusion	SMPS	[94]
Al2O3	Twin screw extrusion	FMPS	[95]
CNFs	Production of composite material, chemical treatment, packaging	CPC & OPC	[96]
MWCNT, Carbon nanopearls	Chemical Vapor Deposition		
Fullerenes, MWCNT	Weighing, mixing & sonicating		
TiO2	Weighing & transferring		
Mn, Ag, Co and Fe oxides	Gas phase condensation reaction		
TiO2 & Ag	Production (Chemical synthesis & ICPA)	SMPS	[97]
TiO2 & SiO2	Handling (Free fall)	ELPI	[98]
TiO2, SiO2, Fe(OH), Al2O3	Handling	FMPS & APS	[99]
OMMT	Handling	FMPS & APS	[100]
SWCNT, MWCNT, Fullerenes, ZnO, TiO2	Handling	OPC, APS, CPC & SMPS	[101]
MWCNTs	Aerosolization by atomizing and shaking	SMPS & APS	[102]
CeO2, TiO2, TiZrAlO, SrCO3	Simulation of pipe leak	SMPS	[103]
Al2O3	Twin screw extrusion	FMPS	[104]

SMPS: Scanning Mobility Particle Sizer; APS: Aerodynamic Particle Sizer; TEOM: Tapered Element Oscillating Microbalance; CPC: Condensation Particle Counter; OPC: Optical Particle Counter; ELPI: Electrical Low-Pressure Impactor; MEAD: Modified Electrical Aerosol Detector; NSAM: Nanoparticle Surface Area Monitor; FMPS: Fast Mobility Particle Sizer; FPSS: Fast Particle Size Spectromer; UNPA: Universal NanoParticle Analyzer

3.2 Machining of Nanomaterials Parts and Usage Phase

Recent studies have shown that nanoparticles get released from polymer-matrix during the functional life cycle of polymer products [108-115]. Not much information is available on this subject. However, in the recent past, researchers have investigated the release of nanoparticles in different mechanical stress situations such as shredding, drilling, sanding, and abrasion of nanocomposites [60,114–116]. These situations are supposed to represent different common machining operations of nanoproducts. Table 2 presents the different release scenarios (for machining and usage phase of nanocomposites and nano-coated materials) that can be found in the literature.

Sachse et al. [117] studied the release of nano-size particles during the drilling of different polyamide-6 nanocomposites. They found that the integration of nanofillers into a polymeric matrix influences the material behaviour, the quantity of particles released during drilling experiments and the physical properties of the nano-sized particles emitted. Addition of nanosilica fillers increased the nano-particles emission by 56 times; however, the nanoclay reduced it by 0.7 times.

Wohlleben et al. studied the effect of manual sanding of different thermoplastic nanocomposites: PA with 4wt.% of nano-SiO_2 and POM with 5.wt% of CNT [110]. It has been shown that the addition of nanofillers into the matrix does not affect significantly the particle size distribution and the surface chemistry of the released particles. Furthermore, non-free nanofillers (i.e. nanofillers embedded in matrix) were found in the dust generated. Similar results were found by Vorbau et al. [116], as significant quantity of nano-particles were not released from ZnO coatings by abrasion. Also, the engineered nanomaterials were still embedded in larger matrix particles.

The addition of CNTs into polymeric matrix also did not significantly modify the concentration of the released nanoparticle, their size distribution and surface area during dry or wet abrasion of nanocomposites [109]. However, differences were found according to samples characteristics such as composite thickness and polymeric matrix type. Also, experimental set-ups are a crucial point in the release of nano-particles. Cutting of nanocomposites was producing higher amount of nano-sized and fine particles in dry conditions. Using water and guard around the rotary wheel allowed significant reduction of exposures to nanoparticles.

Table 2. Release scenarios found in the literature for machining and usage phase of nanomaterials parts

Investigated nanomaterial	Activities	Used equipment	Reference
Composites:			
Polymer/CNT	Dry/wet drilling	FMPS, APS	[108]
Polymer/CNT	Dry/wet abrasive	FMPS,CPC	[109]
POM/CNT, PA/SiO2 & cement/CNT	Sanding , weathering & abrasion	SMPS	[110], [111]
Epoxy/CNT	Abrasion	SMPS	[112]
Polymer/CNT	Burning	ELPI	[113]
Epoxy/CNT	Sanding	CPC	[114]
PP/OMMT	Shredding	DustTrak and FMPS	[115]
PA/OMMT & PA/SiO2	Drilling	SMPS + CPC	[114]
Coatings:			
TiO2, Carbon Black	Sanding	APS, FMPS	[60]
ZnO	Abrasion	CPC, SMPS	[116]
OMMT	Abrasion	CPC, SMPS	[118]
Fe2O3 and ZnO	Sanding	FMPS	[119]
TiO2	Abrasion	ELPI	[120]
TiO2	UV light	SMPS	[121]
CNT	Shaving	FMPS	[75]
TiO2 & Carbon Black nanoparticles	Sanding	FMPS & APS	[122]
SiO2 & CaCO3	Sanding	APS & FMPS	[123]
Powders:			
ZnO & TiO2	Abrasion	SMPS, APS, MOUDI	[124]

FMPS: Fast Mobility Particle Sizer; APS: Aerodynamic Particle Sizer; CPC: Condensation Particle Counter; SMPS: Scanning Mobility Particle Sizer; ELPI: Electrical Low Pressure Impactor; MOUDI: Multi-Orifice Uniform Deposit Impactor.

The release of nano-particles during the usage phase of nanomaterials hadn't been researched in depth. Only few studies about the use of current nanoproducts exist as most of the work is focus on laboratory simulation. For example, Kaegi et al. [125], evaluated the emission of TiO_2 nanoparticles used in the exterior paints. The chemical composition of the samples was investigated by EDX, and bulk chemical analysis was carried out in the runoff samples with the ICP-MS method. They found that a significant quantity of nano-TiO_2 particles can be released into the aquatic environment. This study also showed that the amount of nano-particles released is lower in a two-year old facade than for a freshly painted one.

3.3 Recycling and Waste of Nanomaterials

The risk of engineered nanomaterials' release during disposal and recycling of nanoproducts was evaluated by the Royal Society and Royal Academy of Engineering [126]. Waste incineration and landfill are the most frequent and simplest end of life of waste, and represent 98% of composites disposal [127]. Unfortunately, nowadays no information is available about the behaviour of engineered nanomaterial during this process: how many particles stay in the slag or become airborne, do they degrade due to high temperature, and others important questions remain unanswered [72].

3.4 Identification of Gaps

The actual work, and the studies cited previously contribute to a better understanding of potential exposure but are not able to provide a quantitative assessment of exposure to nanoparticles [89]. Some challenges still need to be tackled.

A complete analysis of all the possible exposure scenarios is necessary. However, the number of cases according to the nanofillers, the matrix used and the process used to release nano-particles (cutting, abrasion, handling, etc) makes this task difficult. Then, it is important to define what parameters influence the release of nanoparticles. For example, as it is shown with this paper [99] with a same process (rotating drum), the size distribution and the total number of particles emitted is dependant of the nanopowder type tested. Processing fumed silica with a rotating drum released around $14.3*10^{-7}$ particles with a mean diameter of 219nm while the same process for ultrafine TiO_2 resulted in a release of $344.8*10^{-7}$ particles with a mean diameter of 200nm.

Also, no standard method exists concerning the measurement and characterization of nanoparticles released during mechanical stress situations. The devices used are different in every study, the chamber, point of measurement also which make it impossible to compare the results obtained in two different studies.

The equipment used in order to estimate the quantity of nanoparticles released in the air is as well a source of error for an accurate measurement. First, the method applied to estimate the size of the particles make the assumption that the particles 'shape is spherical' which is usually not the case. Secondly, the different types of particle counters do not allow the classification nanoparticles according to their composition. This means that the quantity of nanoparticles released can include free engineered nanoparticles, nanoparticles embedded into matrix, agglomerates but also other particles present in nano-size in the environment such as nanoparticles produced by process occurring or naturally present in the atmosphere. It was for example shown that particles under 50nm released during sanding process were mainly due to the sander itself [122] For now, it is necessary to combine 'activity-based monitoring' method with a second method in order to clarify the nature of particles measured [93,95]. Collection, sampling and filtration and analysis of samples allow characterisation of the physic-chemical properties of airborne particles with microscope techniques such as SEM (Scanning Electron Microscopy), TEM (Transmission Electron Microscopy) and XRD (X-ray Diffraction). However, these techniques are long and expensive and applicable with difficulty to real industrial cases. Once again, standardisation of the method is needed.

As mentioned by Yeganeh et al. [79], background noises, due to type of other activities carried out in the plant/lab, number of people present, ventilation, workers techniques, outdoor particle concentrations [79], carbon brushes from different types of machine's motors [76] were often reported as a source of variability in the results. Again, the actual solution is the characterisation of the particles released in order to differentiate the one produced by the materials, and the exterior ones. But this solution does not provide a quantitative result. The other solution is to work in a perfectly clean room or chamber where only the particles induced by the process can be measured but again the perfect or standard method does not exist yet.

4. HEALTH AND SAFETY PRACTICES, STANDARDS AND REGULATIONS

The introduction of a novel technology on the market results in the creation of new gaps in regulations. The Commission of the European Communities evaluated in 2008 [128] that health, safety and environmental risks caused by nanomaterials are currently covered by the legislation under REACH. However, this point of view is not shared by everybody. The European Parliament resolution on regulatory aspects of nanomaterials judged that the current legislation is insufficient and too limited to include the health and safety aspects of nanomaterials [129]. The following part aims to review the actual practices, standards and regulations in relation to nanomaterials in order to evaluate the current situation and gap to focus on in the future.

4.1 Actual Industrial Practices

According to the Project on Emerging Nanotechnologies (PEN) inventory, in October 2013, there were 1628 consumer products based on nanotechnology on market. However, the laws and regulations to control this kind of products and their use were not appropriate, from a Health & Safety point of view, when they arrived on the market. New regulations need to be created and adopted, and this process, which is only at an early stage, will take several years. Helland et al. [57] investigated the actual practices of industries regarding nanomaterials and their risks. A survey was conducted on 40 companies. It was reported that less than 10% investigated the potential risk for environment or human health along a part of the life-cycle of nanoproducts, only 32.5% performed risk assessments where nano particulate materials were involved, and 25% conducted toxicity studies. In general, it was shown that industries were not totally involved in nano particulate materials risks, no standard procedures existed and it was not of high priority for them. Gerritzen et al. [130] reported, following an international survey, that most of the companies dealing with nanomaterials applied safety practices based on conventional practices for chemicals and not specifically on the properties of nanomaterials. Furthermore, this survey showed that companies are expecting industrial and governmental guidance in risk assessment and Health & Safety practices about nanomaterials from the capable authorities.

The importance of the principle of precaution and of safer practices for production and use of nanomaterials was highlighted during several conferences, clusters or workshops concerning nanomaterials (Nanosafe [131], Workshop on the Second Regulatory Review on Nanomaterials [132]). Jamier et al. [58] advised a strategy for production and use of nanomaterials in industry based on two principles of precautionary approach. The first principle was the safety-by-design which consists of the evaluation of risk of nanomaterials at an early stage of product design, and so an adequate choice for materials, design and process of nanoproduct safe for the consumer. However, this will only be possible when data concerning toxicity and risk of nanomaterials will be available. This is a difficult task. There is limited amount of data available on the release scenarios during nanomaterials life cycle. Only a few papers discuss the ways to control the release of nano-sized particles from nanoproducts [133]. Reijnders [133] lists the different options concerning the hazard reduction of release nanoparticles. These include, but not limited to better fixation of nanoparticles in nanocomposites, including persistent suppression of oxidative damage to polymer by nanoparticles, changes of nanoparticle surface, structure or composition, and design changes leading to the release of relatively large particles. The second principle recommended by Jamier et al. [58] is called the ALARA (As Low As Reasonably Achievable) principle and consist of preventive and protective measures to protect workers during nanoobjects and nanomaterials production based on the ones used to reduce and control workers exposure to hazardous aerosols.

4.2 Standards Related to Nanomaterials

Currently, no international standard or agreement exist on the assessment exposure to engineered nanomaterials or on the identification and characterisation of engineered nanomaterials hazards [61]. A guide [134], produced by BSI (British Standard Institute), suggested exposure limits values for different types of nanomaterials, defined by mass:

- Fibrous materials: 0.01 fibre/ml, value realized by scanning electron microscopy;

- Nanomaterials based on carcinogenic, mutagenic or reproduction toxic substances: Exposure limits 10 times inferior for the nanometric substances than for the substances;
- Insoluble nanomaterials: 0.066 times the exposure limits for the chemical substances in micro-sized;
- Soluble nanomaterials: 0.5 times the exposure limits for the micro-form.

However, as it was mentioned previously, a definition of toxicity by mass is not suitable for nanomaterials. The important parameters are size, shape, chemical composition, surface modification and charge, and solubility and persistence.

The European Committee for Standardization (CEN) and the International Organization for Standardization (ISO) are two organisations developing standard and have recently started to work specifically on nanomaterials. Four working groups had been defined by these organisations on this subject in order to split and focus on the most urgent activities [135]:

- Terminology and nomenclature: Define and develop unambiguous and uniform terminology and nomenclature in the field of nanotechnologies to facilitate communication and to promote common understanding;
- Measurement and characterization: The development of standards for measurement, characterization and test methods for nanotechnologies, taking into consideration needs for metrology and reference materials;
- Health, safety and environment: The development of science-based standard in the areas of health, safety and environmental aspects of nanotechnologies;
- Material specifications.

Here is the list of the different documents concerning nanomaterials published at present:

- ISO/TR 27628:2007 – Workplace atmospheres: Ultrafine, nanoparticle and nano-structured aerosols. Inhalation exposure characterisation and assessment.
- ISO/TR 12885:2008 – Nanotechnologies. Health and safety practices in occupational setting relevant to nanotechnologies.
- ISO/TS 27687:2009 – Nanotechnologies. Terminology and definitions for nano-objects. Nanoparticle, nanofibre and nanoplates.
- ISO/TS 12805:2011 – Nanotechnologies. Materials specifications. Guidance on specifying nano-objects.
- PAS 138:2012 – Disposal of manufacturing process waste containing manufactures nano-objects. Guide.
- PAS 139:2012 – Detection and characterization of manufactures nano-objects in complex matrices. Guide.
- ISO/TS 12025:2012 – Nanomaterials. Quantification of nano-object release from powders by generation of aerosols.

The last one is especially interesting, as it describes how to choose the measurement device, and the sampling procedure to follow. However, it only concerns release of nano-objects from powders and not from actual nanoproducts as solid parts undergone mechanical stress situations.

Simulation of the release of nano-sized particles during experimental processes in several studies [99,100,116,118] used some existing standardized procedures. These procedures only concern abrasion and dustiness tests. Moreover, the standards used are the EN-15051 (Workplace atmospheres. Measurement of the dustiness of bulk materials. Requirements and reference test methods) [136] for the dustiness test and the ISO 5470-1:1999 (Rubber- or plastics-coated fabrics. Determination of abrasion resistance. Taber abrader) [137] and the ASTM C1353-07 (Standard Test Method Using the Taber Abraser for Abrasion Resistance of Dimension Stone Subjected to Foot Traffic) [138] for the abrasion tests. These standards only cover the equipment to use and procedure to follow in order to carry out the mechanical tests but don’t mention the measurement of nanoparticles released or their collection.

4.3 Regulations around the World

In 2007, Chaudhry et al. [139] and Fuhr et al. [140] reported the lack of regulation specific to nanotechnology in the European Union, or globally [141], and the fact that they are covered by regulation on conventional chemical substances was denounced. The European Union regulation REACH (Registration, Evaluation, Authorisation & restriction of CHemicals) doesn’t even explicitly refer to nanomaterials. This kind of materials is supposed to be regulated by the fact that they can be covered by the definition of a chemical substance [30]. However, the EU Scientific and Advisory Committees recommends to perform a case-by-case risk assessment on nanomaterials, according to their properties and specific uses [30]. Indeed, the Control of Substances Hazardous to Health (COSHH) regulation which controls the hazardous substances in the workplace is based on Occupational Exposure Limits (OELs) for individual substances. This limit is calculated with the mass of inhaled particles, which is not relevant for nanomaterials as it's now known that the toxicity of nanoparticles is related to their size [96,126,142,143]. Moreover, nanomaterials are still not classified as new substances under the EINECS (European Inventory of Existing Commercial Substances) but are considered as the same substances as the bulk version [144]. The lack of information concerning nanomaterials tends to change as the European Chemicals Agency (ECHA) published a guidance on information requirements and chemicals safety assessment, including recommendations for nanomaterials in 2012 [145].

In European Union, some directives regulate manufacturing and commercialization of any products [31,146–148]. Safety and health of workers at workplaces is defined by the EU directive 89/391/EEC [148] to ensure a high level of protection to workers during their work by implementation of preventive measures. This includes exposure to nanomaterials through hazardous substances. The Council Directive 98/24/EC [147] presents the protection of workers at work against the risks caused by chemical agents and the obligations related to identification and assessment of risk due to use of hazardous chemical agents. Nanomaterials are not mentioned in this document. Also, every consumer product is subject to the General Product Safety Directive [31], which imposes risk assessment on their environmental impact and contains provisions for health and safety of workers, consumers, patients, and users. Nanomaterials have to follow this regulation. Concerning the disposal and waste, the Directive 2006/12/EC [146] defined which waste as hazardous, and settle down obligations on Member States to ensure that the waste treatment is safe regarding human health and environment. Again nanomaterials are not clearly specified. Current legislation is supposed to cover the risk on human health and environment along the life-cycle of every product. However, as nanomaterials are not referenced, current practice can be insufficient.

Other governments, outside European Union, show an interest for this topic. Several reports published by organisations from United States stated the importance of nanosafety for the success of nanotechnology [149,150]. Also, in United States, the Environmental Protection Agency (EPA) works for the implementation of a Significant New Use Rule (SNUR) which intend to increase the available data about nanomaterials risks and safety. Any entities intending to manufacture or process new nanoproducts has to submit a basic set of information (chemical identification, material characterisation, physical/chemical properties, commercial use, production volume, exposure and fate data, and toxicity data) to the EPA at least 90 days before the beginning of the activity [151]. Concerning wastes and end-of-life, two laws regulate these issues in United States: RCRA (Resource Conservation and Recovery Act) [152], and CERCLA (Comprehensive Environmental Response, Compensation, and Liability Act) [153]. In theory, these laws cover nanomaterials and nanowastes. However, they were judged to be inappropriate [105] for example products containing nanomaterials can be considered as household waste and so, non-hazardous. The Environmental Protection Agency recommends implementation of these laws [105], concerning the possibility to classify specific nanowastes, as hazardous wastes, and the need of research in order to determine if the existing practices for disposing and treating bulk forms of solid wastes are appropriate for the nano forms of similar chemicals.

Several others reports have been published [154–157] concerning the lack of knowledge and regulations about nanomaterials and their uses and Kuhlbusch et al. [56] reported the urgent need of standardization for test procedures simulating workplace activities and processes. The Second Regulatory Review on Nanomaterials, published by the European Commission, concluded that one of the actual priorities is to establish validated methods and instrumentation for detection, characterisation and analysis in order to complete information on hazards of nanomaterials and develop methods to assess exposure to nanomaterials [128].

5. NANOSAFETY: FUTURE PERSPECTIVES

5.1 Nanosafety Related Projects

The European Commission is investing money in naosafety related research. The Sixth Framework Programme included 13 projects concerning nanosafety for a budget of €31 million [68] and one of the 7 priority thematic area was 'Nanotechnologies and nanosciences, knowledge-based functional materials, new production processes and devices [158]. Following FP6, the 7th Framework Programme for Research and Technological Development was conducting from 2007 to 2013 with an overall budget over €50 billion [159]. Again, one of the ten key thematic areas is orientated to nano-research: 'Nanosciences, nanotechnologies, materials and new production' [159]. Through this programme 34 nanosafety orientated projects were financed with a budget of €106 million [68]. The members of the Nanosafety Cluster concluded that these projects allowed to increase the production of data concerning the potential hazard of Engineered Nanomaterials [68]. However, they also raised a number of unknown points to work on [68]:

- The need of information related to exposure of Engineered Nanomaterials and safety of nanoproducts during their life-cycle still exists;
- Standardized methods to assess the exposure of Nanoparticles and reference materials for toxicity assessment are a priority for the future research;
- Interactions between Nanomaterials and environment and living systems need to be assessed and understood.

Projects focused on these objectives are currently running. FP7 carries on research by founding two projects, MARINA and NanoValid until the end of 2015. MARINA (MAnaging RIsks of Nanomaterials) aims to develop and validate a risk management method for nanomaterials by developing tools to assess the state-of-the-art and the risk management strategy around four areas: Materials, exposure, hazard and risk [160]. On its side, Nano Valid project has also for objective to improve risk and life cycle assessment of nanomaterials including methods for the fabrication, physiochemical characterisation, hazard identification, exposure assessment and dispersion control and labelling of engineered nanomaterials [161]. In the same idea, FP7 financed QNano project grouping the most important nanotechnology, medicine and natural sciences facilities in order to improve and develop nanosafety assessment [162].

Through LIFE programme [163], existing since 1992, the European Commission also founded several nano-related projects. During the last 3 years, 8 projects concerning nanomaterials were launched, and all of them raise question about environmental and safety aspects of nanomaterials. SIRENA project [164] (SImulation of the REIease of NAnomaterials from consumer products for environmental exposure assessment) is part of this programme. This project aims to demonstrate and validate a methodology to simulate the unintended release of nanomaterials from consumer products by replicating different life cycle scenarios to be adopted by a wide number of industrial sectors in order to get the necessary information for exposure assessment. Thanks to this project, a new experimental set-up had been developed, reducing the issues mentioned earlier, in order to measure airborne particles released during drilling or milling of nanocomposites in a control environment and obtain repeatable data set. The device is composed of a chamber, a CNC machine, and a SMPS+C for the measurement of the airborne particles. Pre-filter, HEPA filter (H14) and a fan are used to provide constant clean air inside the chamber. The CNC machine allows to have precise control of feed rate and rotation speed of the drill, and thus to have reproducible and repeatable tests. Also, a water cool spindle drill is used in order to avoid background noise produced by the drilling motor.

Also, the EU Framework Programme for Research and Innovation, Horizon 2020 [165] has the intention to fund several projects related to the assessment of release and fate of nanomaterials with the coordination of several Small and Medium Sized Enterprises through the Nanotechnologies, Advanced Materials, Advanced Manufacturing, and Processing, and Biotechnology area [166].

5.2 Key Areas for Future Research

The members of the Nanosafety Cluster defined 4 key area of research for the next 10 years [68]:

- Nanomaterials identification and classification. Classification should either be done by shape, composition/chemistry, complexity/functionality, or biointerface;

- Nanomaterials exposure and transformation. Exposure and behaviour of nanomaterials needs to be assessed along the life-cycle, from the production to the end-of-life, and covering handling, use and aging;
- Hazard mechanisms related to effects on human health and environment. Research has to be focus on understanding toxicity including grouping, translocation and clearance of nanomaterials, and behaviour regarding vulnerable populations and environment. This is a real challenge considering that nanoparticles can interact with living systems at molecular or cellular levels;
- Tools for predictive risk assessment and management including databases and ontologies. Standardization of risk assessment method of nanomaterials is the key point of a successful progress of research in this field.

6. CONCLUSION

Nanomaterials are one of the most promising material technologies and the use of nanocomposites is increasing exponentially. However, this explosive increase in their use has caught the regulating authorities by surprise, and they are playing catch up, albeit slowly. The Health and Safety aspects and potential risks of this new technology still need to be studied in depth to ensure their continued success.

The current regulations, to some extent, cover the use of nanomaterials. However, the risks of nanomaterials are defined according to two factors: Toxicity and exposure. Toxicity of nanomaterials was found to be dependent on different parameters: Shape, size, chemical composition, surface modification and charge, and solubility and persistence. This is not in line with the classical chemical substances for which the toxicity is defined by mass. The current legislations and regulations classify toxicity of nanomaterials in proportion to the toxicity of their bulk substances. Thus, a change of regulations specific to nanomaterials is necessary.

There is a dearth of regulation when it comes to exposure to nanomaterials later in the product life cycle. Engineered Nanoparticles are different from nanoparticles released during ageing or mechanical stress/shear failure of a nanocomposite. The assessment of toxicity and exposure need to be done through the whole life-cycle of products, and a complete analysis of all the possible exposure scenarios is necessary and should be part of any future regulations. Also, standard methods need to de developed in order to have comparable and repeatable results. This paper highlights this gap in literature and regulations and introduces the work done in project SIRENA. Project SIRENA aims to develop a robust and repeatable experimental set-up in order to assess various mechanical failure scenarios for nanocomposites leading to exposure to nanomaterials that may have undergone physico-chemical changes during their life cycle (as part of a nano-composite). The data generated from this project will be used to device some of the regulations related to exposure and toxicity.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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