NanoImpact 14 (2019) 100149

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact

Assessing occupational risk in designs of production processes of nano-materials

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ARTICLE INFO

Keywords:
Safety-by-design
Nano-safety
Nanomaterials
Control banding
Occupational risk

ABSTRACT

Building safe production places can protect workers more effectively than managing risks in a plant that has been conceived without taking into account safety upfront. In this paper, we describe an approach to assessing potential risks already at the stage of design of production processes of nano-enabled products. In a chemical plant, risk results from the combination of hazard of the chemicals and exposure of workers to them. Toxicological profiles of novel nanomaterials, however, are generally unknown; in addition, the impossibility of measuring exposure in a plant that does not exist yet exacerbates the challenge of designing safe production processes. This paper describes a simple method to formulate realistic hypotheses about the toxicity of untested nanoparticles and derives a simplified model of exposure that enables non-specialists (e.g., managers, engineers) to analyze potential risks in projects of future production plants. As an example of analysis of risk in the absence of experimental data, the paper describes the procedure to generate maps of risks of two envisaged production chains of antibacterial textiles: 1) sonochemical synthesis and deposition of bactericidal nanoparticles, and 2) spray deposition of suspension of bactericidal nanoparticles.

1. Introduction

Designing safe processes for the production of nano-materials can protect workers more effectively than managing risks that emerge only after a plant has been built. In a chemical plant, risk results from the combination of the toxicity of a compound and its likelihood to penetrate into the human body (i.e., exposure). The toxicity of novel nanoparticles, however, is generally unknown, and the impossibility to estimate exposure in a plant that does not exist yet exacerbates the challenge of minimizing risk in an envisaged production process.

Traditional chemical and pharmaceutical industries manage risk through the definition of Occupational Exposure Limits (OEL) that correspond to the highest tolerable atmospheric concentrations of specific compounds. These OELs are established on the basis of accurate epidemiological studies that involve hundreds, if not thousands, of workers over many years. This approach cannot be used to assess risks in a hypothetical plant for the manufacturing of nano-materials: epidemiological data for nanoparticles are not yet available, and, even if they were, establishing OELs would be extremely difficult, if not impossible, because toxicity of nanoparticles depends also on non-quantifiable parameters such as shape, or surface reactivity (Mu et al., 2014; Verma and Stellacci, 2010). (OELs have been defined only for a small number of nanoparticles (Kuempel et al., 2012).) Driven by innovation, industry pursues the development of innovative nanomaterials for which even data for in-vitro toxicity are not available, or not conclusive.

Over the last decades, data about the in-vitro toxicity of nanoparticles have been published for a number of nano-particles, and the understanding of many aspects of the interaction of nanoparticles with cells that result in adverse mechanisms (Mu et al., 2014; Verma and Stellacci, 2010; Limbach et al., 2007; Liu and Hurt, 2010; Auffan et al., 2009) has provided the basis for the development of methods for non-experimental assessments of the toxicity (Puzyn et al., 2011; Zhang et al., 2012; Gajewicz, 2017a; Marvin et al., 2017; Mu et al., 2016). These methods include physical-chemical modeling (Puzyn et al., 2011; Zhang et al., 2012), data mining (Gajewicz, 2017a; Mu et al., 2016; Gajewicz, 2017b), and probabilistic inference (Marvin et al., 2017; Sheehan et al., 2018). At the same time, concerns about the new risks arising from the manufacturing of nano-materials and regulatory requirements have spurred the detailed modeling of exposure: key factors that determine the rates of transport of potentially hazardous nanomaterials from a source to a receptor have been identified and described (Tielemans et al., 2008; Zalk et al., 2009; Cherrie and Schneider, n.d.; Van Duuren-Stuurman et al., 2012; Paik et al., 2008).

In this paper, we exploit this knowledge to formulate hypotheses about hazard of nanoparticles of unknown toxicity and to estimate

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https://doi.org/10.1016/j.impact.2019.100149
Received 8 November 2018; Received in revised form 6 February 2019; Accepted 25 February 2019
Available online 12 March 2019

Table 1
Summary of rules to assign hazard scores.

Reported values of EC_{50} ($mol \cdot L^{-1}$)	Stability	Shape	Composition	Hazard score
$\log EC_{50} \leq -3$	Release of ions	Fibers $> 5\,\mu m$	Contains known toxic elements (e.g., Pb, Cd, Hg)	10
$-3 < \log EC_{50} \leq -2$	Reactive surface			7
$\log EC_{50} > -2$	Inert		Inert coating	4

exposure in plants that will be developed at a pilot scale and that, for the moment, exist only on paper. As a practical implementation of our strategy, we show how, even in the absence of experimental data, maps of risk can be generated along the production chain of textiles functionalized with antibacterial nanoparticles in two production processes: 1) sono-chemical synthesis of nanoparticles on textile fibers (Perelshtein et al., 2016); and 2) spray deposition of dispersion of nanoparticles. These maps can support managers and engineers in the decision process that leads to a future safe and efficient production plant.

2. Experimental design

2.1. General approach: banding of risk

We defined *Risk* as a variable whose values were given by the product of values of *Hazard*, a variable that quantified the toxicity of individual nanoparticles, and values of *Exposure*, a variable that estimated the amount of nanoparticles that reach a worker during a given process (Eq. (1)):

$$\text{Risk} = \text{Hazard} \times \text{Exposure} \quad (1)$$

Once the value of risk has been calculated for a given nanoparticle at a specific step of the production chain, it will be assigned to a category (or, band) of risk defined as an interval of values of risk (See following sections.) These bands will then be used to rank, or prioritize, risk along the production chain. Values of Hazard and Exposure were defined as dimensionless scores that ranked expected levels of toxicity and concentrations.

2.2. Determining hazard scores of nanoparticles

2.2.1. Background on the toxicity of nanoparticles

Although many details of the interaction of nanoparticles with biological organisms are not yet understood, the following physical-chemical parameters are recognized to be important drivers of toxicity: size, shape, degree of dissolution, surface charge, surface reactivity, and bulk reactivity (Mu et al., 2014; Verma and Stellacci, 2010; Auffan et al., 2009)

Size and shape influence transport rates of nanoparticles and determine the rates at which the body uptakes and, eventually, expels them (Mu et al., 2014). The degree of dissolution of these particles is also crucial, because it alters the bio-availability of potentially toxic ions. Surface charge has emerged as another important parameter, because it determines the strength of the interaction of a nanoparticle with the cellular membrane; positively charged particles result much more toxic than negatively charged (Verma and Stellacci, 2010). A nanoparticle can also catalyze a number of reactions within the cell; reactive surfaces can induce a state of oxidative stress that eventually kills the cell. The chemical composition of the nanoparticles must also be taken into account: oxidative and reductive dissolution results from the reaction of biological redox couples with the components of nanoparticles, which are then dissolved into the cellular medium (Auffan et al., 2009). When these properties are known for a given nanoparticle, they can be used to deduce its (expected) level of toxicity. When this type of information is partially, or not at all, available, values of key parameters can be estimated through physical-chemical modeling (Puzyn et al., 2011; Zhang et al., 2012). A non-experimental assessment of the toxicity of a nanoparticle can be based on the following general considerations: toxicity tends to decrease with increasing oxidation number (Z) of the cation that compose the nanoparticle; values of $Z > 3$, however, may become unstable and react inside the cell. Nanoparticles composed of stable reducible oxides, that is, oxides that exhibits reduced cations at defect sites (e.g., CeO_2), tend to be less toxic than those composed of oxidizible oxides (i.e., oxides that exhibit defects that lead to oxidized cations, such as NiO).

2.2.2. Definition of an arbitrary range of values for the hazard of nanoparticles

We have defined an arbitrary scale of hazard that goes from 4, roughly corresponding to Classes 0–1 of the Diamond Classification System of Chemicals, up to 10 assigned to nanoparticles expected to be very toxic, and corresponding, roughly, to classes 3–4 of the Diamond Classification System. The minimum score of hazard is set to 4 (and not, for example, to zero) for two reasons: 1) zero hazard would result in a zero risk in any condition, including extremely high exposure, which is unrealistic; 2) inert nanoparticles, which usually exhibit very low levels of toxicity in-vitro (i.e., in the short term) may persist in an organism and give rise to some form of toxicity over the long term (Laux et al., 2017). Toxicity induced by bio-persistence has not been thoroughly investigated yet.

2.2.3. General criteria for assigning hazard scores

Table 1 lists a series of empirical rules to assign a hazard score to a nanoparticle. Reported values of EC_{50}, the dose of nanoparticles that reduces the availability of cells by 50% in in-vitro cultures, give already an indication of the toxicity of a nanoparticle. A review of published data indicates that the values of this parameter varies over 4 orders of magnitude, as a result of several adverse mechanisms (Puzyn et al., 2011; Zhang et al., 2012; Kaweeteerawat et al., 2015). In Table 1, we identified three levels of toxicity defined as ranges of values of EC_{50} (measured in $mol \cdot L^{-1}$ of nanoparticle); to each level, we assigned a specific hazard score. The chemical stability in a biological environment is another indicator of the potential toxicity of a nanoparticle. We assigned the highest hazard score (10) to nanoparticles that are known, or expected on the basis of their composition, to release ions through oxidative, reductive, or hydrolytic dissolution. Another group of potentially toxic nanoparticles are those with reactive surfaces. These nanoparticles exhibit generally values of EC_{50} lower than those observed for nanoparticles that dissolve; the reason of this difference is that only the species at the surface of the nanoparticle are active (for surface active nanoparticles, the dose to be considered should be surface area and not mass or number.) To this category, we assigned the intermedium hazard score 7. Inert nanoparticles were assigned the score 4. Nanoparticles composed of species of known high toxicity (e.g., Pb, Cd, Hg) were assigned the highest hazard score, while nanoparticles potentially toxic but bearing an inert, or non-toxic, stable coating fell in the lowest hazard group (score = 4). When some of these informations are not available for a given nanoparticle, hazard can be assigned based on information from similar compound, or from non-experimental assessments.

2.3. Criteria for assigning exposure scores

Exposure is the amount of a compound that reaches the human body from an emission point. Managing risk in a chemical plant deals mostly with controlling exposure: the risk arising from the processing of a very toxic compound is low if exposure is kept low. Theoretical assessments of occupational exposure (Paik et al., 2008; Schneider et al., 2011; Tielemans et al., 2011) are based on the source-to-receptor model, which essentially determines exposure as resulting from the combination of rate of emission of nanoparticles from one, or more, point-sources, from their transport toward the receptor (i.e., the worker), and from the characteristics of the receptor (e.g., behavior, or type of protection of the worker); both the physical-chemistry of the nanoparticles and the characteristics of the production process determine the rate of emission and transport toward the receptor.

Validated implementations of the source-to-receptor model have identified sources and mechanisms that determine exposure in an industrial production plant (Tielemans et al., 2008; Cherrie and Schneider, n.d.; Van Duuren-Stuurman et al., 2012; Schneider et al., 2011; Tielemans et al., 2011; Marquart et al., 2008). Inhalation is the most common mechanism for a hazardous chemical to penetrate into the human body. The physical-chemical properties of a compound determine its intrinsic airborne probability, mainly due to dustiness for powders and vapor pressure for liquids. In a plant manufacturing materials with high airborne probability, these materials can be found in the air regardless of the specific characteristic of the process, and can linger in the atmosphere, as background concentration, well after a production cycle has been concluded. Some specific type of processing or handling, however, can expose the worker to additional amounts of nanoparticles. Manual handling, for example, puts the worker in contact with the hazardous materials, which can then reach also skin and mouth. Spraying of dispersion of nanoparticles, a type of processing that we consider in this work, generates aerosols also of compounds with low intrinsic airborne probability and, eventually, add to the background concentration. Ultimately, unpredictable events can expose a worker to additional amounts of the dangerous chemical; among these events we can cite fire (the most common cause of industrial accidents), rupture of a tank, undetected leakage, human errors, earthquakes. In these cases, it is evident that high amounts of chemicals handled or stored represent an additional potential source of exposure. Exposure, however, depends also on time through duration and frequency (i.e., rate of repetition in a given time) of a specific operation. These consideration lead to the definition of exposure as the sum of three independent emissions (i.e., intrinsic airborne probability, type of processing, and amount handled) multiplied for the total time (i.e., frequency and duration) of operation (Eq. (2)):

$$\text{Exposure} = [(\text{Intrinsic Airborne Probability}) + (\text{Amount of } NP) + (\text{Type of Processing})] \times (\text{Frequency of Operation}) \times (\text{Duration of Operation}) \quad (2)$$

We did not try, however, to quantify exposure: to each term of Eq. (2), we assigned dimensionless scores that ranked the emission potential of each source of exposure at each step of a specific production process. To assign these scores, we distilled concepts of validated approaches into simple rules that avoid any computational complexity (Van Duuren-Stuurman et al., 2012; Schneider et al., 2011; Tielemans et al., 2011; Marquart et al., 2008) so that non-specialists (e.g., managers, engineers) can understand and apply them. These rules are discussed in details in the following sections.

2.3.1. Intrinsic airborne probability

It is the fraction of a compound that lingers in the air and that workers can inhale; for solids, it is strictly related to dustiness (Schneider et al., 2011), which, in turn, depends on the physical state of the compound. Table 2 summarizes the rules, derived from advanced models (Zalk et al., 2009; Van Duuren-Stuurman et al., 2012; Paik et al., 2008), for assigning scores on the basis of the physical state of the compound. We assigned the highest score (10) to powders and volatile liquids. We did not take into account variations of airborne probability of powders caused by different levels of humidity that can change dustiness, because, for a plant that does not exist, humidity is undefined. We assigned an intermediate score to granulates (5); although granulates have a very low dustiness, we assigned this intermediate score because fine powders are often associated to granulates; brittle flakes fall in this category as well. We set to 1 the score for liquids (reagents, solutions, and dispersion) and firm granulates because they have a very low dustiness.

Table 2
Criteria for assigning scores for intrinsic airborne probability of nanoparticles.

Physical state	Intrinsic airborne probability score
Powders	10
Volatile liquids	10
Granulates, flakes	5
Firm granulates	1
Liquids, dispersions	1

2.3.2. Amounts of nanoparticles and other reagents processed

Intuitively, the total amount of a processed or stored material determines the amount that can reach a worker. In line with other models (Van Duuren-Stuurman et al., 2012; Paik et al., 2008), for this component we chose the scores listed in Table 3. For dispersions, the amount to be considered is the amount of nanoparticles dispersed in the total volume of liquid used.

2.3.3. Frequency of operation

This descriptor originates from the consideration that rare events pose much lower risks than frequent ones. As such, for each step of the production chain, the number of repetition of the process contributes to exposure. Table 4 shows the criteria for assigning scores for frequency; also these criteria were adopted according to available models for exposure (Zalk et al., 2009).

2.3.4. Duration of operation

The time required for an operation of the production chain also contributes to the total exposure. Very long processes increase risk for workers even if they are handling materials of low toxicity. Table 5 reports the rules for assigning scores for duration (Adapted from Ref (Zalk et al., 2009)).

2.3.5. Processing

This descriptor takes into account contributions to the total exposure that originate from specific processing and considers four scenarios: 1) Manual Handling (e.g., feeding of reagents, emptying bags, transfer of finished products); 2) Active Stimuli, that is, those necessary for the main process (e.g., sonication, shaking, heating, spaying, stirring); 3) Passive Stimuli, that is, stimuli that assist the main process but that are not necessary (e.g., mechanical processing, drying, rolling); and 4) no Stimuli (Table 6.)

We assigned the maximum score (10) to Manual handling because it implies the direct contact of the worker with the chemical. Some types

Table 3
Criteria for assigning exposure scores for amounts of nanoparticle processed.

Amount	Amount score
> 100 mg	10
11–100 mg	5
< 10 mg	1

Table 4
Criteria for assigning exposure scores based on frequency of processing of nanoparticles.

Frequency	Frequency score
Daily	10
Weekly	7
Monthly	4
> 1 Month	1

Table 5
Criteria for assigning exposure scores based on duration of operation.

Duration	Duration score
> 4 Hours	10
1–4 Hours	7
30–60 min	4
< 30 min	1

Table 6
Criteria for assigning exposure scores for processing of nanoparticles.

Processing	Processing score
Manual	10
Active stimuli	10
Passive stimuli	5
No stimuli	1

of Active Stimuli (or direct stimuli such as ultrasounds for sonochemical synthesis and deposition of the nanoparticles, and spraying in spray-coating) lead to a high probability for the worker to get in contact with potentially toxic materials; use of ultrasounds, in fact, promotes the aerosolization of the dispersion of the nanoparticles. High temperature is another type of stimulus that induce aerosolization of liquids as well as vigorous shaking, and spraying. Processing that assist the main process, but that is not necessary, includes mechanical shaking, rolling, drying. This type of processing (Passive, or indirect, stimuli) can induce the aerosolization of particles at lower levels than direct stimuli, because they do not act on the chemicals being processed, and, for this reason, we assigned them the intermedium score 5. Absence of stimuli does not contribute to the final exposure, and we assigned them the minimum score 1.

2.4. Definition of bands, or categories, of risk

Now that the criteria for estimating Hazard and Exposure have been established, it is possible to calculate risk (i.e., Hazard × Exposure) at each step of the production chain of a nanomaterial. Before we do that, however, we must define bands (that is, ranges, or categories) that will rank risk; in other words, we have to define what high, low, or medium risk are. From the definition of Hazard and Exposure given in the previous sections, it follows that values of risk range between 30.000, given by the product of the highest possible value of exposure, 3.000 (obtained by substituting the highest values for scores for each term in Eq. (2) (10 + 10 + 10) × 10 × 10 = 3.000) with the highest hazard score 10, and the lowest values of 12 (that is, 4 (lowest hazard) × 3 (lowest exposure, from (1 + 1 + 1) × 1 × 1). Within this range, we defined three bands of risk: 1) High Risk, for risk scores in the range 30.000–11.550; 2) Medium Risk, for risk scores in the range 11.550–6.600; and 3) Low Risk, for risk scores < 6.600 (Table 7.) The High Risk band covers hazards between 10 and 7 considered at the highest and intermedium exposure (i.e., 1.650). Medium risk corresponds to hazards between 7 and 4 at intermedium exposure. Finally, exposures < 1.650 to nanoparticles with hazard score < 7 fall within the Low Risk band.

Table 7
Definition of the bands of risk.

Defining ranges of values of Eq.1	Band of Risk
30.000 ≤ Risk ≤ 11.550	High Risk
11.550 < Risk ≤ 6.600	Medium Risk
<6.600	Low Risk

3. Results

We will apply the process highlighted in the previous sections to analyze risk in the production of textiles functionalized with antibacterial nanoparticles. We consider two alternative processes that will be implemented in pilot plants: 1) Sono-chemical synthesis of the nanoparticles directly on the fibers (Perelshtein et al., 2016), and 2) spray-coating of the textiles with a dispersion of nanoparticles synthesized elsewhere.

3.1. Hazard scores for a series of bactericidal nanoparticles

We hypothesized that the plants for which we want to assess risk already at the design stage will process different types of nanoparticles: inorganic oxides, carbon dots, core-shell oxides, and organic polymers. This spectrum of chemical compositions and structural characteristics ensures that several bactericidal mechanisms will be tested on the textiles. Based on published data, candidate bactericidal nanoparticles are:

1. ZnO;
2. $Zn_xCu_{1-x}O$;
3. CuO;
4. Ga@C-Dots (Ga-doped Carbon Dots);
5. TiO_2-shell/SiO_2-core;
6. PPy (poly-pyrrole).

There are no studies about the toxicity in-vivo of these compounds for humans. We will assess their toxicities and assign hazard scores based on published in-vitro studies (when available), reported antibacterial activity, and physical-chemical properties. Table 8 reports our assessments that we describe in the next sections. Before we delve into the details, however, let us observe that the task that these compounds are expected to complete informs already about their potentially harmful biological activity: the more effectively these nanoparticles will kill bacteria, the more toxic they should be expected to be. Regardless of their specificities, our starting hypothesis is that these nanoparticles are all toxic to some degree.

Table 8
Hazard scores for bactericidal nanoparticles based on their expected toxicities.

Nanoparticle	Hazard score
ZnO	10
CuO	10
$Zn_xCu_{1-x}O$	10
TiO_2/SiO_2	7
Ga doped C-Dots	7
Poly-Pyrrole	7

ZnO. Hazard Score = 10. Zinc oxide nanoparticles are known to dissolve partially in in-vitro experiments; Zn^{2+} ions are toxic. Values of EC_{50} (i.e., the dose that kills 50% of the cells) for *E. coli* exposed to ZnO has been reported to be as low as 10^{-4} mg·L^{-1}. The release of toxic ions is the main bactericidal mechanism, which, however, has been shown to be harmful also for human cells (Puzyn et al., 2011; Zhang et al., 2012; Tielemans et al., 2011) in in-vitro tests. Non-experimental methods (Puzyn et al., 2011; Sheehan et al., 2018) foresee a high toxicity for this type of nanoparticles.

CuO. Hazard Score = 10. Results of in-vitro studies about the toxicity of this oxide are very similar to those for ZnO. CuO, as other oxides of metals with formal valence ≤2, can dissolve up to 10% in a biological environment (Puzyn et al., 2011; Zhang et al., 2012; Tielemans et al., 2011). In addition, Cu^{2+} ions are electrochemically active and can catalyze the synthesis of Reacting Oxygen Species inducing an oxidative stress that can kill the cell (Auffan et al., 2009).

$Zn_xCu_{1-x}O$. Hazard Score = 10. There are no studies available about the in-vitro toxicity of this mixed oxide. (and it would be very difficult to obtain consistent results for this nanoparticles due to the variability of the composition.) Assuming that it would behave like ZnO and CuO, we assigned the highest hazard score to this mixed oxide. It is very likely, in fact, that this oxide will dissolve in a biological environment because the oxidation number of both cations is 2. In addition, Cu^{2+} could induce oxidative stress that is harmful for the cell.

Ga@C-Dots. Hazard Score = 7. There are no data available for carbon dots doped with gallium, and we assigned the hazard score on the basis of information available for un-doped C-Dots and other carbonaceous compounds. Carbon is known to be non-toxic; carbon dots are generally considered of low toxicity (Li et al., 2012). Over the long term, however, the toxicity of this type of nanoparticle can be due to the reactivity of their surfaces, to the size of the particles of carbon, and to the presence of traces of Ga. It has been shown that macrophages cannot eliminate the finest particles of carbon black, which, in fact, induce inflammation in the respiratory tract (Aam and Fonnum, 2007). C-Dot have been observed to penetrate the cellular membrane and accumulate in the cytoplasm where they became cytotoxic (Cao et al., 2007; Hong et al., 2018). Gallium is a reactive metal that, if released in the cytoplasm, can initiate some redox catalytic cycle that produces reactive oxygen species. Being also photoactive (Li et al., 2012), we expect that the toxicity (as well as its bactericidal power) of these doped C-Dots increases when irradiated (Meziani et al., 2016). Conservatively, we assigned an hazard score of 7.

TiO_2-shell/SiO_2-core. Hazard Score = 7. TiO_2 and SiO_2 are two very stable and bio-persistent oxides. There are no studies, however, about the toxicity of these two oxides over a long time. Assuming that the toxicity of the core-shell particle is due exclusively to the outer layer, we assigned an hazard score of 7 corresponding to the toxicity of a bulk TiO_2 nanoparticle. TiO_2 nanoparticles are effective photo-catalysts whose bactericidal action can be switched on and off by UV light (Liu et al., 2014); irradiated TiO_2 nanoparticles induce oxidative stress (Jovanović, 2015).

Poly-pyrrole Nanoparticles (PPy). Hazard Score = 7. Poly-pyrrole nanoparticles are obtained from the oxidative polymerization of pyrrole units (Balint et al., 2014). The polymer can be oxidized to different degrees, and the resulting positive charge can be stabilized through delocalization on the conjugated system; this positive charge could interact with the cellular membrane and disrupt it; this mechanism could explain the bactericidal action of this type of nanoparticles, and inform about their potential toxicity. Studies that tested poly-pyrrole as a scaffold for drug delivery did not report any significant cytotoxic effect (Au et al., 2011). It has been observed, however, that the cytotoxicity of PPy depends on the preparation protocol (Balint et al., 2014): the oxidative polymerization of pyrrole requires reactive reagents that can be of different type and that remain embedded into the polymeric nanoparticles; these contaminants (often metal ions) might catalyze the production of reactive oxygen species once in the cytoplasm. We did not assign the minimum hazard score to PPy because the presence of these active ions is very likely.

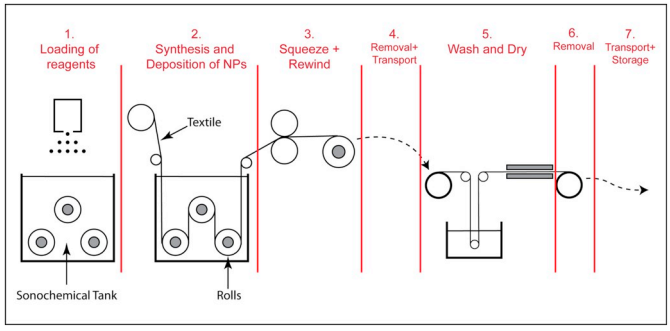

Fig. 1. Schematic representation of the pilot plant for continuous sonochemical functionalization of textiles with bactericidal nanoparticles.

3.2. Analysis of risks in the design of a roll-to-roll sonochemical plant

3.2.1. Description of the process

Fig. 1 displays the sequence of operations of the production of antibacterial textiles in a Roll-To-Roll sonochemical prototype plant. In order to calculate risks of this production line, the scores of the components of exposure (that is, airborne probability, amount, duration, frequency, and processing) must be estimated at each step. Table 9 summarizes the results of this evaluation that we describe in the following sections.

3.2.2. Exposure scores at each step of the production chain

3.2.2.1. Step 1. Loading the sonochemical tank with reagents. Sonochemical synthesis and deposition of bactericidal nanoparticles use reagents that are powders (Intrinsic Airborne Probability score = 10). Specifically, ZnO and CuO nanoparticles are obtained from sonochemical degradation of the acetates of the corresponding cations, and these acetates are known to be very toxic (Perelshtein et al., 2016). Workers introduce high amounts (~ 25 g, Amount score = 10) of the reagents into the sonochemical tank manually (Processing score = 10). The operation is repeated almost every day (5 days per week; frequency score = 10). Overall, feeding the reagents takes < 30 min (Duration score = 4). Considering all these factors, the Exposure score for Step 1 calculated through Eq. (2) is 1.200 (that is, (10 + 10 + 10) × 4 × 10).

3.2.2.2. Step 2. Synthesis and deposition of nanoparticles. Sonochemical synthesis and deposition occurs in aqueous solution of reagents (Perelshtein et al., 2016) (Intrinsic Airborne Probability score = 1.) In a first design, the volume of solution processed should amount to 170 L and contain ~15 g of nanoparticles, which we considered a very high amount (Amount score = 10). A major contribution to the overall exposure comes from the processing component; ultrasounds, which are active stimuli, induce the aerosolization of a portion of the dispersion of the nanoparticles (Processing score = 10). Duration of this step falls in the range 1–4 hours (Duration score = 7). All these contributions yield an overall exposure for step 2 of 1.470. (Table 9.)

3.2.2.3. Step 3. Squeeze and rewind of the functionalized textile. After the nanoparticles have been deposited, the functionalized wet textile is squeezed. At this point, the textile should be loaded with 0.5–1% in weight with nanoparticles (Amount score = 1.) The process is fully automated. Release of nanoparticles might occur through mechanical shaking at the rolls, or from the accidental dripping of the reaction dispersion (passive stimuli; Processing score = 5). We calculated an overall exposure for Step 3 of 490.

Table 9
Scores of the component of exposure for the roll-to-roll sonochemical plant.

Step (Fig. 1)	Description	Intrinsic airborne probability	Amount	Duration	Frequency	Processing	Exposure score
1	Loading reaction tank with reagents	10 (Powders)	10 (> 20 g)	4 (30-60 min)	10 (4 days/week)	10 (Manual)	1.200
2	Sonochemical synthesis and deposition of nanoparticles	1 (Dispersion)	10 (170 L)	7 (1-4 h)	10	10 (Active stimuli. Ultrasounds)	1.470
3	Squeeze and recoil	1 (wet NP)	1 (0.5–1 wt%)	7	10	5 (Passive stimuli. Aerosolization through mechanical shaking)	490
4	Removal wet coated fabric	1	1	4	10	10 (manual handling)	480
5	Transport to and mounting of the wet coated fabric to the wash/dry machine	1	1	4	10	10 (manual handling)	480
6	Washing and dry	10	1	7	10	10 operation in open air	1470
7	Removal and transport of the coated fabric to stock station	10	1	4	10	10 (manual handling)	840

3.2.2.4. Step 4. Removal of the wet textile. Workers remove the squeezed textile and transport it to the drying station manually (Processing score = 10). Considering the small amount of nanoparticles anchored to the textile, and their very low dustiness (the textile is still wet), the exposure score resulted to be 480. (Table 9.)

3.2.2.5. Step 5. Transport of wet textiles to wash and dry station. For this step, we calculated an overall exposure of 480. This score originated mainly from the high score for processing (10; workers remove the dried coil manually); airborne probability is very low because, at this stage, the textile is wet (Intrinsic Airborne Probability score = 1).

3.2.2.6. Step 6. Washing and drying. Washing and drying are automated processes that do not expose workers to nanoparticles. Processing score, however, was set to 10 because these operations occur in open air; the amount of nanoparticles deposited on the textiles is very low (0.5–1% wt). At this step, however, dried unbound nanoparticles behave like fine powders that workers can inhale (Intrinsic Airborne Probability score = 10). This operation is repeated 4 days per week (Frequency score = 10). We calculated an overall exposure of 1.470.

3.2.2.7. Step 7. Removal and transport of the coated fabric to stock station. Manual transport and storing of dried functionalized textile lead to an exposure score of 840.

3.3. Banding of risk for the roll-to-roll sonochemical plant

Estimation of hazard and exposure for the sonochemical plant makes it possible to calculate the risk matrix (Table 10) for this process, given by the product of Hazard score of nanoparticles (Table 8), and exposure scores as calculated in the previous section (Table 9). The values of risk obtained made it possible to identify the band (or level) of risk for each step of the process.

We observe that the first and last two steps expose workers to the highest risks. These high risks arise from the combination of the hazard of the nanoparticles, and the high exposure determined mainly by the high airborne probability (first two steps) and by manual handling, which puts workers in direct contact with the hazardous chemicals and nanoparticles.

3.4. Analysis of risk for the spray coating pilot plant

3.4.1. Description of the process and estimation of exposure step-by-step

This plant should use ultrasound nozzles to spray-coat textiles with the type of nanoparticles listed in Table 8. Fig. 2 displays the five steps of the hypothesized process. In contrast with the sonochemical plant, nanoparticles to be sprayed are either purchased as powders, or synthesized in an independent reactor, which requires a separate analysis of risk. In the following, we discuss the details of the computation of exposure at each step of the process; Table 11 summarizes results.

3.4.1.1. Step 0. Synthesis of nanoparticles in a separate reactor. When synthesized in house, nanoparticles are produced in a 650 L tank, separated from the spraying station. Reagent are powders (Intrinsic Airborne Probability score = 10) handled manually by workers (Processing score = 10). Synthesis lasts < 4 h, and it is repeated once per week. Total exposure for this step is 210. In case the plant processes commercial formulation, this step would be ignored.

3.4.1.2. Step 1. Loading the nanoparticles tank. Workers load the nanoparticle tank connected with the nozzles manually (Processing Score = 10). The tank can contain up to 10 L of dispersion of nanoparticles (~5 g. Amount score = 10). For this operation, we estimated a total exposure score of 84 (Details given in Table 11.)

3.4.1.3. Step 2. Spray coating. Aerosolization through ultrasounds nozzles (Fig. 2) results in a high probability for the worker to inhale nanoparticles. The plant can spray up to 170 L of dispersion of nanoparticles per day (< 4 h). These factors sum up to a total exposure of 210.

3.4.1.4. Step 3 to step 5. After the nanoparticles have been deposited on the fibers, the probability that they can reach and penetrate the body of workers is very low, even when the finished rolls are removed and stored manually (Table 11.)

3.4.2. Risk matrix for the spray coating plant

Table 12 reports the risks computed for the spray coating plant. The color code makes it easy to identify the most risky steps (Red and Orange blocks). Ultrasounds aerosolization (Step 2) and synthesis of nanoparticles (Step 0), when required, lead to the highest risks mostly because they involve manual handling or high airborne probability of the materials being processed. After the nanoparticles have been anchored to the textiles, risk falls either in the intermedium or low risk band.

4. Conclusion

4.1. A simplified model of hazard and exposure enables an assessment of risk in the absence of experimental data

More than a method, in this paper we have outlined a thinking-process for reducing uncertainty about risk in plants that exist only on paper as projects for future manufacturing of nano-enabled products.

Table 10
Risk matrix for the roll-to-roll sonochemical plant. Values of risk at each step are given by the product of hazard (reported next to each nanoparticle) and exposure scores reported as calculated in Table 9. Colors identify the band of risk as defined in Table 7.

	1 (Exp: 1.200)	2 (Exp: 1.470)	3 (Exp: 490)	4 (Expos: 26)	5 (Exp: 480)	6 (Exp: 1.470)	7 (Exp: 840)
Ga@C-Dots (Haz:7)	Medium (risk=8400)	Medium (risk=10290)	Low (risk=3430)	Low (risk=3360)	Low (risk=3360)	Medium (risk=10290)	Low (risk=5880)
ZnO (Haz: 10)	High (risk=12000)	High (risk=14700)	Low (risk=4900)	Low (risk=4800)	Low (risk=4800)	High (risk=14700)	Medium (risk=8400)
CuO (Haz: 10)	High (risk=12000)	High (risk=14700)	Low (risk=4900)	Low (risk=4800)	Low (risk=4800)	High (risk=14700)	Medium (risk=8400)
SiO_2@TiO_2 (Haz: 7)	Medium (risk=8400)	Medium (risk=10290)	Low (risk=3430)	Low (risk=3360)	Low (risk=3360)	Medium (risk=10290)	Low (risk=5880)
$Zn_xCu_{1-x}O$ (Haz:10)	High (risk=12000)	High (risk=14700)	Low (risk=4900)	Low (risk=4800)	Low (risk=4800)	High (risk=14700)	Medium (risk=8400)

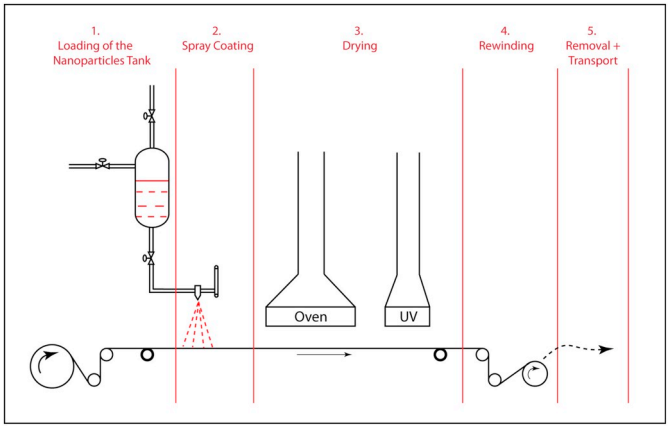

Fig. 2. Design of the spray-coating process showing the steps for which exposure and risk have been calculated. Step 0, synthesis of nanoparticles, is not showed.

There are no data available for the toxicity of nanoparticles that will be processed in these plants, but the combination of the analysis of their chemical behavior, information about their biological activity, and knowledge of the behavior of particles with analogous structure and composition made it possible to anticipate what type and which degree of toxicity should be expected for these compounds. A simplified model of exposure seats at the core of our strategy, which is based on the estimation of five distinct contributions: airborne probability and amount used of nanoparticles, frequency and duration of operation, and type of processing (Eq. (2)). The impossibility of experimental characterization of emission and transport of nanoparticles prevented us from using detailed models of exposure such that elaborated by Schneider and co-workers (Schneider et al., 2011) or the Advanced REACH Tool (ART) (Tielemans et al., 2011); the map of risk as those we have generated for the two processes analyzed in this paper, however, provide important information to managers and engineers about potential risks in the future plant and can support decisions that consider safety in the further development of the project.

4.2. From risk banding to control banding

The strategy of banding risk, that is, the definition of categories of risk as ranges of values of hazard and exposure (Eq. (1)), can still be applied to manage risk once the plant will be built. Each band of risk, in fact, can be associated to a series of controls, or actions, designed to minimize risk (i.e., Control Banding). Chemical and pharmaceutical industries use this strategy for managing risk through the elaboration of detailed controls that, for each band, or category describe unambiguously i) Personal Protective Equipment of the workers; ii) Containment Level of the chemicals; iii) General Ventilation of the plant; iv) Local Exhaust Ventilation at crucial places; v) Maintenance, cleaning, and waste disposal; vi) Characteristics of Surfaces (e.g., floor, walls); vii) Industrial Hygiene Monitoring, and viii) other General Actions. (Ref (Naumann et al., 1996) reports detailed description of these controls). This approach has been proposed also for managing risk in plants that manufacture nanoparticles (Van Duuren-Stuurman et al., 2012; Paik et al., 2008; Liguori et al., 2016; Eastlake et al., 2016). While designing the plant, however, the advantages of adopting controls over alternative designs of the process can be considered and evaluated; if needed, realistic estimation of exposure through advanced tools (Schneider et al., 2011; Tielemans et al., 2011) might be attempted at production steps falling into the high risk band. Let us emphasize that Eq. (2) used in this paper gives a dimensionless score which we used to rank exposure: Eq. (2) does not estimate exposure, and, for this reason, it cannot be used for regulatory purposes. Realistic models of exposure, however, bear conceptual complexity and computational burden that are too time consuming at a design stage and require a number of detailed information that are not available at a design stage.

4.3. Designing safe manufacturing plants

We have described a conceptual process for the assessment of risk in designs of plants for manufacturing nano-enabled materials. This process (we hesitate to call it a method) cannot be automated and

Table 11
Scores of the components of exposure and overall exposure for the spray-coating pilot plant.

Step (Fig. 2)	Description	Intrinsic airborne probability	Amount	Duration	Frequency	Processing	Exposure score
0	Synthesis of nanoparticles *(Ignore when commercial formulation are used)*	10 (Powders)	10 (Reaction tank > 650 L)	7 (1-4 h)	10	10	2100
1	Loading of the nanoparticles tank.	1 (Dispersion)	10 (10 L > 600 mg)	4 (30-60 min)	10	10 (Manual)	840
2	Spray coating	10 (Aerosol)	10 (170 L)	7 (1-4 h)	10	10 (Ultrasounds + Aerosolization)	2100
3	Drying	1 (wet NP)	1 (0.5–1 wt%)	7	10	1 (Automated)	210
4	Recoiling of the functionalized textile	1	1	4	10	5 (External stimuli. Mechanical shaking)	280
5	Removal and Transport of the finished textile	1	1	4	10	10 (Manual)	480

Table 12
Risk matrix for the Spray Coating plant. Values of risk correspond to the products Hazard × Exposure. Colors identify bands of risk.

	0 (Exp: 2100)	1 (Exp: 840)	2 (Exp: 2100)	3 (Exp:210)	4 (Exp: 280)	5 (Exp: 480)
Ga@C-Dots (Haz:7)	High (risk=14700)	Low (risk=5880)	High (risk=14700)	Low (risk=1470)	Low (risk=1960)	Low (risk=3360)
ZnO (Haz: 10)	High (risk=21000)	Medium (risk=8400)	High (risk=21000)	Low (risk=2100)	Low (risk=2800)	Low (risk=4800)
CuO (Haz: 10)	High (risk=21000)	Medium (risk=8400)	High (risk=21000)	Low (risk=2100)	Low (risk=2800)	Low (risk=4800)
SiO_2@TiO_2 (Haz: 7)	High (risk=14700)	Low (risk=5880)	High (risk=14700)	Low (risk=1470)	Low (risk=1960)	Low (risk=3360)
$Zn_xCu_{1-x}O$ (Haz:10)	High (risk=21000)	Medium (risk=8400)	High (risk=21000)	Low (risk=2100)	Low (risk=2800)	Low (risk=4800)
PPy (Haz:7)	High (risk=14700)	Low (risk=5880)	High (risk=14700)	Low (risk=1470)	Low (risk=1960)	Low (risk=3360)

outsourced, for example, to a software. Assigning some scores for hazard and exposures involved considerations specific to the production step we were analyzing and that may not hold in other processes; different (or multiple choices) were possible. We were not able to elaborate detailed rule for estimating hazard and preferred an holistic approach that integrates general experimental evidences of the toxicity of nanoparticles and physical-chemical considerations; in some cases, some of our estimations may be judged (legitimately) too conservative, in others, some subjective considerations could not be avoided due to broad uncertainty. Despite its limitation, our approach based on reasoning about hazard and exposure rather than on their accurate quantification provided information that managers and engineers can use in choosing the most effective strategy to safeguard future workers.

Acknowledgement

This work was supported by the European Union's Horizon 2020 research and innovation programme through the project “PROTECT,” number 720851.

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