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Controlling the risks of nano-enabled products through the life cycle: The case of nano copper oxide paint for wood protection and nano-pigments used in the automotive industry

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ABSTRACT

The widespread use of engineered nanomaterials (ENMs) in consumer products and the overwhelming uncertainties in their ecological and human health risks have raised concerns regarding their safety among industries and regulators. There has been an ongoing debate over the past few decades on ways to overcome the challenges in assessing and mitigating nano-related risks, which has reached a phase of general consensus that nanotechnology innovation should be accompanied by the application of the precautionary principle and best practice risk management, even if the risk assessment uncertainties are large. We propose a quantitative methodology for selecting the optimal risk control strategy based on information about human health and ecological risks, efficacy of risk mitigation measures, cost and other contextual factors. The risk control (RC) methodology was developed in the European FP7 research project SUN and successfully demonstrated in two case studies involving real industrial nano-enabled products (NEPs): nano-scale copper oxide (CuO) and basic copper carbonate ($Cu_2(OH)_2CO_3$) used as antimicrobial and antifungal coatings and impregnations for the preservation of treated wood, and two nanoscale pigments used for colouring plastic automotive parts (i.e. red organic pigment and carbon black). The application of RC for human health risks showed that although nano-related risks could easily be controlled in automotive plastics case study with modifications in production technology or specific type of engineering controls, nano-related risks due to sanding and sawing copper oxide painted wood were non-acceptable in the use lifecycle stage and would need the identification of a more effective risk control strategy.

1. Introduction

Nanotechnology is one of the Key Enabling Technologies identified in the European Union (EU) 2020 Strategy, which is expected to enhance industrial performance and encourage competitiveness across several sectors such as healthcare, electronics, energy, construction, and transportation (COM(2009)512; COM(2012)341). Along with the optimistic projections about the potential of nanotechnology to promote innovation and economic prosperity, the widespread use of engineered nanomaterials (ENMs) has raised concerns in regulators, industry and insurance professionals about their safety to human health and the environment (Hristozov et al., 2016; Bos et al., 2015). This has triggered sustained investment of European research funding for over a decade toward assessing the environmental and human health risks of key ENMs that are commonly used in workplace settings and in consumer products. These efforts have generated an enormous amount of data and an array of experimental and modelling tools to study the physicochemical properties, fate, exposure and hazard of ENMs. However, these data are often insufficient for regulatory assessment in terms of quality, which calls for targeted data curation efforts. Such efforts have been ongoing in a variety of European research projects (e.g. NANoREG, NanoReg 2, GRACIOUS), which will improve the quality

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and completeness of the available data, but more time is needed before these data will become available to stakeholders to be effectively used for regulatory decision making. Moreover, the feasibility study for performing regulatory risk assessment of ENMs has identified serious gaps in our fundamental understanding of nano-bio interactions, modes of action and adverse outcome pathways. This renders the resulting risk estimations to be based on poorly established assumptions that fail to support decision making for risk management (Hristozov et al., 2016). Although the discussion on ways to overcome some of the above challenges has not be settled yet, there is a general agreement that in order to proceed with innovation through nanotechnologies in the context of highly uncertain risks, the Precautionary Principle can guide the assessment of human health and environmental risks and the implementation of robust risk control strategies through the lifecycle of nano-enabled products (NEPs). In order to address some of these barriers, within the European FP7 research project SUN, we developed the Risk Control (RC) module which is part of the Decision Support System (SUNDS) (Subramanian et al., 2016). This module supports the assessment and management of human health and ecological risks and the selection of suitable risk management measures, such as engineering control, personal protective equipment and/or administrative procedures, which can reduce non acceptable risks to acceptable values. Moreover, the systematic collection of information on hazard, exposure, risks and risk management measures effectiveness can guide the process of designing suitable Safe-by-Design (SbD) alternatives i.e., technological alternatives that modify the NEPs properties to either reduce the release of ENMs from the product, or to induce their accelerated alteration/degradation in relevant biological and/or environmental media in order to decrease their persistence, bioaccumulation and toxicity, while maintaining their intended functionality (Costa, 2014).

The specific objectives of this research paper are: i) to present the Risk Control (RC) module of the SUNDS system, which includes the SUN project's nano-specific inventory of Technological Alternatives and Risk Management Measures (TARMM) (Oksel et al., 2016) and ii) to demonstrate its application in two real industrial case studies involving nano-scale copper oxide and basic copper carbonate used as antimicrobial and antifungal coatings and impregnations, and two nanoscale pigments used for colouration of plastic automotive parts. More specifically, the demonstration focused on controlling human health risks as estimated ecological risks were acceptable for both case studies (Semenzin et al. in preparation).

2. Methods

2.1. SUNDS risk control methodology

The SUNDS RC methodology can estimate occupational, consumer, public health and environmental risks posed by engineered nanomaterials (ENMs) along their lifecycles, including industrial nano-enabled products (NEPs). Risks are assessed in either deterministic or probabilistic terms, and are considered unacceptable when exposure exceeds prescribed no-effect threshold, or, ultimately, where the risk characterization ratio (RCR) is greater than or equal to 1. In situations where risks are not sufficiently controlled, the RC module guides the user in selecting suitable Technological Alternatives and Risk Management Measures (TARMMs) based on information about their efficacy and costs. Detailed description of the underlying Human Health Risk Assessment (HHRA) and Ecological Risk Assessment (ERA) methodologies is out of the scope of this paper and can be found elsewhere (Pizzol et al., 2019; Hristozov et al., 2018; Tsang et al., 2017; Pang et al., 2017; Semenzin et al., (in preparation). Therefore, these approaches are only briefly outlined in the next sections, while the focus of this paper is on the methodology used for aggregation and classification of the risk assessment results (Sub-section 2.1.1) and the selection of adequate TARMMs (Sub-section 2.1.2).

2.1.1. Aggregation and classification of the risk assessment results

The HHRA methodology can assess occupational, consumer and public health risks along the lifecycle of the assessed NEP, by integrating outputs from: a) the exposure assessment which consists of site-specific measurements (when available) or results from the application of exposure models (e.g. NanoSafer CB tool (Jensen et al., 2013), ConsExpo nano (Delmaar et al., 2006), iEAT (Gorman Ng et al., 2012; Gorman Ng et al., 2016), and b) the hazard assessment which estimates acceptable human dose/concentration levels below which a substance does not adversely affect human health. Both assessments can produce deterministic and/or probabilistic estimates depending on information availability. In the case of humans exposed through the environment, an exposure model estimating Predicted Environmental Concentrations (PECs) in different environmental compartments is used instead (Semenzin et al., in preparation).

The ERA methodology can assess risks for key environmental compartments such as surface water and soil (e.g. natural, urban or sludge). Ecological risk for each life cycle stage is calculated by integrating outputs from: a) an environmental exposure model providing PEC values and b) deterministic procedures or probabilistic Species Sensitivity Distributions (SSDs) that estimate Predicted No Effect Concentrations (PNECs) for various species in an environmental compartment (ECHA, 2015). The resulting ecological risk estimate is either deterministic (i.e. PEC/PNEC ratio) or probabilistic (i.e. the percentage of RCR distribution greater or equal than 1).

For both HHRA and ERA, SUNDS can simultaneously assess risks for different lifecycle stages, targets, and routes of exposure. A single combination of a lifecycle stage, a target and a route of exposure (e.g. a worker in the synthesis lifecycle stage exposed to nanomaterials through inhalation) was called lowest unit of assessment (LUA) (Pizzol et al., 2019). Once risks are estimated for each LUA, an aggregation functionality implemented in the software produces a single risk value for each lifecycle stage (i.e. synthesis, formulation, use and end of life) as well as for the entire lifecycle, considering all relevant targets, activities and routes of exposure. The aggregated risks are then classified according to a default risk classification, which was derived by expert elicitation via a web-based questionnaire (see Supplementary information of Pizzol et al. (2019), for details) and follows this nomenclature:

- *Acceptable* or *Non-acceptable* in the case of deterministic risks (considering the risk characterization ratio (RCR) below or above one, respectively);
- *Acceptable*, *Needs Further Consideration* or *Non-acceptable* in the case of probabilistic risks (as explained below).

Aggregation in HHRA may be additive, in the case of risks related to the same target, or non-additive, in the case of risks related to different targets for the same lifecycle stage, as presented in details in Hristozov et al. (2018) and Pizzol et al. (2019). The default classification profile for deterministic Human Health (HH) risk uses the 95th percentile of the risk characterization ratio distribution to identify Acceptable (when the threshold of one (i.e. the acceptable risk) is higher than the 95th percentile) and Non-acceptable risks (threshold of one below the 95th percentile). The default classification profile for probabilistic HH risk includes the following three classes: Acceptable (when the threshold of one (i.e. the acceptable risk) is higher than the 95th percentile of the risk characterization ratio distribution), Needs Further Consideration (threshold of one between the 90th and the 95th percentile) and Non-acceptable (threshold of one below the 90th percentile). The selection of the percentiles for this pre-defined risk acceptability classification profile can be changed depending on specific assessment needs as for example more vulnerable targets to be accounted for. New percentile values can be directly inserted in the RC module and used instead of default values.

Aggregation of LUA in ERA is always non-additive because PEC and

PNEC are highly dependent upon physico-chemical transformation, fate, transport, exposure and species within an environmental compartment and thus, risks for different environmental compartments cannot be added. According to the questionnaire results (available as Supplementary information, Section 1) and in agreement to the HHRA methodology, the approach consists of selecting the maximum risk to represent each life cycle stage and the entire life cycle.

The default classification profile for deterministic ecological risk uses the 95th percentile of the risk characterization ratio distribution to identify Acceptable (when the threshold of one (i.e. the acceptable risk) is higher than the 95th percentile) and Non-acceptable risks (threshold of one below the 95th percentile). Probabilistic ecological risk can be obtained if either exposure (e.g. based on probabilistic material flow analysis) or effect values (e.g. based on SSDs), or both, are represented by a probability curve (Gottschalk et al., 2013). The default classification profile for probabilistic ecological risks includes three classes: Acceptable (when the threshold of one is over the 99th percentile), Needs Further Consideration (threshold of one between 95th and 99th percentile), and Non-acceptable (threshold of one under the 95th percentile).

2.1.2. Selection of adequate TARMMs

Once HHRA and ERA have been performed for each life cycle stage, risks that are non-acceptable or needing further consideration have to be controlled through the application of suitable TARMMs, as shown in Fig. 1. In order to support the selection of suitable TARMMs to be applied case by case, a database of TARMMs with their efficacy and cost was constructed from four sources: Exposure Control Efficacy Library (ECEL) 1.0 (Fransman et al., 2008), Advanced REACH tool (ART) (Fransman et al., 2011; Tielemans et al., 2011), TARMM inventory (Oksel et al., 2016) and the review by Goede et al. (2018). Specifically, a set of TARMMs included in these sources were selected by exposure assessment experts for their applicability for exposure control of NEPs through their life cycle, considering the following aspects: study design of measurement (in case of data derived from literature or real exposure measurements), data quality, ENM type, exposure route (inhalation/dermal/oral), physical state (solids/liquids), life cycle stage, workplace control measures (including specifications about the type of sampling (stationary or normal) and the source typology (e.g. powder, solid matrix, suspension, on surface)). The resulting inventory contains the following types of TARMMs: engineering controls, respiratory protective equipment and dermal protective equipment (i.e. RMMs only). As TAs (Technological Alternatives) are rather ENM and NEP specific, they are not included in the database, but guidance is provided on how they can be evaluated for risk control. In the TARMM database, for each RMM the following application conditions are reported: ENM type including identity and life cycle stage (i.e. pristine nanomaterial, fragment with embedded nanomaterial, fragment with protruding nanomaterial, nanomaterial agglomerate), particle size distribution, efficacy (single value or range) and cost (single value or range) (Goede et al., 2018).

TARMMs are implemented in accordance with the standard hierarchy of control strategies in order to eliminate hazard or to reduce exposure (NIOSH Report, 2013). The traditional hierarchy of controls describes the order that should be followed when choosing between viable options for controlling risks in a reliable and cost effective manner: 1) Elimination, 2) Substitution, 3) Engineering controls, 4) Administrative and Work practice controls, 5) Personal Protective Equipment (PPE), as explained below. When nano-specific efficacy values are available for the TARMMs belonging to the options listed above, they are used by the RC module to automatically re-calculate the LUA-specific risks in real time in order to show whether the adopted measures would reduce those to acceptable levels.

According to the traditional hierarchy of controls, the most effective approach to eliminate hazard is by SbD technological alternatives that modify the NEPs properties to either reduce the release of ENMs from the product, or to induce their accelerated alteration/degradation in relevant biological and/or environmental media in order to decrease their persistence, bioaccumulation and toxicity, while maintaining their intended functionality (Costa, 2014). Examples of SbD strategies

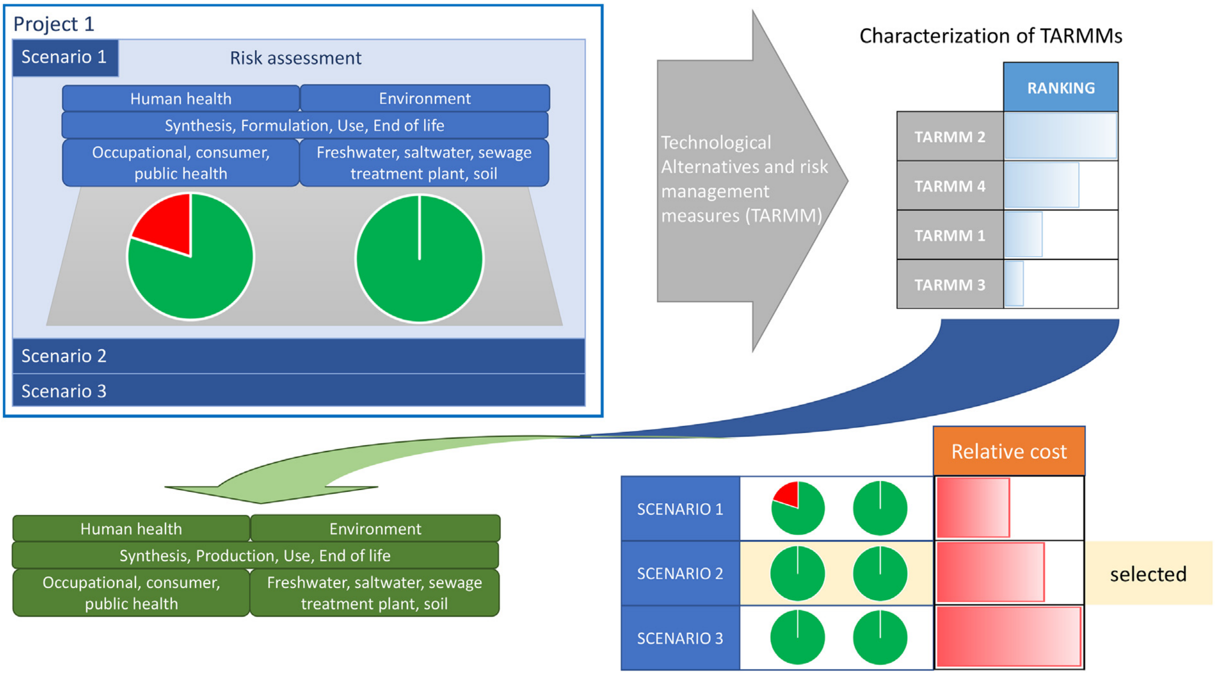

Fig. 1. Schematic representation of the Risk Control methodology implemented in SUNDS. The process starts from the risk assessment results of a specific nano-enabled product, estimated for both human health and the environment along the product life cycle (Scenario 1). Based on such results, suitable TARMMs are ranked according to their efficacy in reducing hazard and/or exposure in the LUAs for which Non-acceptable risks were identified. The user can then select one or more TARMMs to create new scenarios (e.g. Scenario 2 and 3) in which those TARMMs are applied and residual risks are estimated. The selection of the desirable scenario is made according to both residual risk and cost of TARMMs.

include surface modification (e.g. coating, surface functional groups) and embedding the ENM in matrices (Costa, 2014; Morose, 2010; Caruso, 2001). If suitable SbD strategies (i.e., technological alternatives) are available for the investigated material, the system compares their efficacies and costs to other relevant TARMMs in order to propose the most optimal risk control strategy.

Risk reduction can also be accomplished by limiting potential exposure, which is a more common approach than applying SbD strategies. In the case of occupational exposure, TARMMs need to be linked to the attributes of the exposure scenario corresponding to non-acceptable risk. Some relevant occupational exposure attributes include activity/process and material characteristics (e.g. solid matrix, on the surface, suspension, powder, spray, mechanical, dispersion/formulation). In order to estimate cost of implementing a TARMM, several factors may be relevant such as task frequency and duration, and the number of people involved in the task.

Key TARMMs to mitigate consumer risk, particularly in the case of novel materials, are consumer information labels; and their effectiveness can be operationalized as a measurement of improved safety behaviour or consumer risk perception. For example, surveys can be used to quantify to what extent a consumer label was successful in encouraging effective risk management behaviours in a population or influenced it to perceive risks with more nuance (Purmehdi et al., 2017). However, this is context-specific information and is not provided in the TARMM database but can be added by the user. The cost of consumer labels could include the cost of label development like manpower, analytical tests, etc. Some occupational TARMMs (e.g. specialized spray cans to control release, gloves, protective clothing) may be applicable also in the consumer context for specific NEPs.

RC can be implemented for ecological and public health risks by linking risks that need to be mitigated to TARMMs such as ventilation systems (decrease in exposure concentration through dilution mechanisms), scrubbers (decrease in exposure concentration through absorption mechanism) and others. Reduction of emissions from the source or emission systems translate to lower exposure or transmission to environmental compartments.

Selection of TARMMs to be applied is supported by utilizing LUAs. Each TARMM is characterized by a list of LUAs where it is applicable; by comparing this applicability list with the list of LUAs presenting Non-acceptable or Needs Further Consideration state it is possible to provide a list of suitable TARMMs, ordered by the number of LUAs they could improve.

The user can then decide to simulate the application of one or more (sets of) TARMMs (thus building new scenarios, as depicted in Fig. 1) in order to check their cost and efficacy in controlling unacceptable risks.

As far as the RC cost estimation is concerned, each TARMM can be applied in one or more LUAs thus requiring the identification of the number of items to be applied along with the single item duration and cost. The total cost of RC is obtained by multiplying the single item cost by the number of items for each TARMM and then performing a weighted sum of TARMMs' costs by using a weight that normalizes all TARMMs durations to the maximum TARMM duration, as reported below:

$$C_{TOT} = \sum_{t \in T} (c_t \cdot n_t) \cdot w_t$$

$$w_t = \frac{\max_{i \in T} d_i}{d_t}$$

where C_{TOT} is total cost of RC, T is the set of selected TARMMs, t is a single TARMM, c_t is cost of a single item for TARMM t, n_t is the number of items for TARMM t, w_t is the duration adjusted weight for TARMM t, d_i is duration of TARMM i and d_t is duration of TARMM t.

Cost of the single item for each TARMM is derived by internet search and expert elicitation. Cost information is often available as a range of values owing to numerous brands available, various specifications to which TARMM can be set (e.g. engineering controls) as well as the difficulty to monetize some inputs (e.g. SbD) or do so in a comparable way (e.g. long term investment versus consumables). Expert elicitation is helpful to derive cost, as a single value wherever possible, to enable comparison of TARMMs, in terms of commonly used brands, appropriate specifications and approximate cost estimates. If the user has more specific, real costs, those can be directly inserted in the RC module and used instead of default values.

As far as the efficacy in controlling unacceptable risks is concerned, in the TARMM database efficacy is defined as follows (Goede et al., 2018):

2.1.2.1. *For Engineering controls*

$$\text{Reduction (efficacy) factor} = \text{C}_{\text{control on}}/\text{C}_{\text{control off}};\ \text{OR C}_{\text{after/with}}/\text{C}_{\text{before/without}}$$

$$\text{Effectiveness (\%)} = 1 - \text{Efficacy factor} * 100,\ \text{OR } (\text{C}_{\text{without/off}} - \text{C}_{\text{with/on}})/\text{C}_{\text{Without/off}} \times 100$$

2.1.2.2. *For Respirators, gloves, protective clothing.*

$$\text{Protection factor,PF} = \text{C}_{\text{outside}}/\text{C}_{\text{inside}};\ \text{OR C}_{\text{upstream}}/\text{C}_{\text{downstream}},\ \text{OR C}_{\text{without}}/\text{C}_{\text{with}}$$

$$\text{Penetration/migration (\%)} = \text{C}_{\text{inside}}/\text{C}_{\text{outside}} * 100,\ \text{OR C}_{\text{upstream}}/\text{C}_{\text{downstream}} * 100$$

$$\text{Effectiveness (\%)} = 1 - (\text{C}_{\text{inside}}/\text{C}_{\text{outside}}) * 100$$

where C = exposure concentration.

As for costs, if the user has more specific, real efficacy values, those can be directly inserted in the RC module and used instead of default values. Efficacy values are therefore used to simulate the application of one or more (sets of) TARMMs, by adequately reducing exposure to ENMs according to TARMM-specific efficacy and therefore estimating residual risks for each new scenario. According to obtained residual risks (i.e. whether they are acceptable or not) and estimated RC cost for each scenario, the user can proceed with the selection of the preferred scenario (i.e. the preferred (set of) TARMM(s) to be implemented in the specific case).

2.2. *Case study products*

The proposed methodology has been applied in two real case studies: 1) nano-scale copper oxide (CuO) and basic copper carbonate ($Cu_2(OH)_2CO_3$) used as antimicrobial and antifungal coatings and impregnations for the preservation of treated wood, and 2) nanoscale pigments used for colouration of plastic automotive parts (i.e. red organic pigment and carbon black).

2.2.1. *Nano-scale CuO and $Cu_2(OH)_2CO_3$ used as antimicrobial and antifungal coatings and impregnations*

2.2.1.1. Case study description. Wood preservation treatment is indispensable to increase the service life of timber by imparting it with bactericidal, fungicidal and insecticidal properties (Freeman and Mcintyre, 2013; Lebow, 2010). Copper based formulations have been widely used for several years, particularly in ground contact applications to treat timber due to their effectiveness as a biocide and relatively low mammalian toxicity (Pizzol et al., 2019; Hristozov et al., 2018; Lebow, 2010; Freeman and Mcintyre, 2013). While impregnation of wood using pressure treatment is the most effective way to achieve good copper penetration and retention, superficial treatments are also applied for consumer-based applications (Lebow, 2010). Such treatments include non-pressure impregnation (e.g. brief dipping, cold soaking and steeping, diffusion processes, vacuum processes) and in situ treatments (e.g. surface treatments using spraying, brush and paste application, installation of internal diffusible chemicals, internal fumigant treatments) (Lebow, 2010).

This case study presents the results of nano-scale copper oxide (CuO) and basic copper carbonate ($Cu_2(OH)_2CO_3$) along the lifecycles of antimicrobial and antifungal coatings and impregnations. It simulates two decision contexts. The first concerns a manufacturer that has to implement risk control for a hypothetical nano-copper oxide (n-CuO) acrylic wood-preserving coating applied as paint by brushing to protect a wood facade through its life cycle. In addition to weathering protection provided by conventional acrylic paint, the n-CuO paint also provides a biocidal functionality (especially decay by soft rot fungi) to the softwood cladding. The n-CuO used in the paint has a particle size of 3–35 nm and it is mixed with an acrylic base to produce the nano-enabled paint. The second decision context concerns a manufacturer that has to implement risk control for a basic copper carbonate ($Cu_2(OH)_2CO_3$) impregnation solution applied to wood for constructing e.g. garden fences, decking, playgrounds. The basic copper carbonate is wet milled until it reaches nano-sized grade. Then, n-$Cu_2(OH)_2CO_3$ is combined with water, stabilizers, and co-biocides to make the stock solution. The wood impregnation is typically carried out in steel cylinders or retorts. The wood is loaded on special tram cars and moved into the retort, which is then closed, evacuated and subsequently filled with preservative solution. Then pressure forces the preservative into the wood until the desired amount is absorbed.

2.2.1.2. Input information. The first category of inputs required for the application of the RC methodology to this case study is presented in Table 1, where the assessed HH risk scenarios and the related risk results are reported. Further details on the HHRA application can be found in Hristozov et al. (2018) who applied the SUNDS HHRA methodology to the case study to estimate occupational risk and consumer risk for 13 exposure scenarios in the four lifecycle stages of the n-CuO acrylic paint and basic copper carbonate ($Cu_2(OH)_2CO_3$) (i.e. synthesis, formulation, use, end of life). Most of the 13 assessed exposure scenarios present negligible exposure, while for six of them (i.e. two exposure scenarios considering inhalation for workers (ES2 and ES4), one considering dermal contact for workers (ES4), one considering inhalation for consumer (ES4), one dermal contact for consumer (ES4) and finally one considering oral exposure for consumer (ES11)), the risks have been estimated as reported in bold in Table 1. Indeed, according to Hristozov et al. (2018), the use of basic copper carbonate ($Cu_2(OH)_2CO_3$) impregnation does not pose any non-acceptable risks in all the assessed scenarios, with the only exception of the exposure scenario related to children exposed directly to the treated wood by skin contact (ES11).

On the basis of the classification system described in Section 2.1.1, non-acceptable risks have been identified and highlighted in red cells in Table 1 (sixth column).

To apply risk control options to mitigate the risks that are non-acceptable or need further consideration, available TARMMs relevant to the assessed exposure scenarios were collected from industry and exposure assessment experts. For each of them, efficacy was derived by calculating the average of experts' approved literature values included in the TARMM database. This information is summarised in Table 1, at columns 7th and 8th. Similarly, costs of TARMM used to control risks of n-CuO paint are described in Table 1, at columns 9th and 10th.

For the exposure scenario related to children exposed directly to the treated wood by skin contact, transfer of copper to the mouth and related ingestion, no engineering control or personal protective equipment can obviously be applied and therefore residual risk was not calculated. In this case, the potentially most effective measures to be considered involve SbD measures to reduce the release potential and/or the hazard of the material as well as consumer labelling and safety instructions (as anticipated by Hristozov et al., 2018).

2.2.2. Nanoscale pigments for colouration of plastic automotive parts

2.2.2.1. Case study description. The use of plastics in interior, exterior, and under bonnet components of automobiles reduces their weight, and improves aesthetics, vibration and noise control, and cabin insulation (Research and Markets Report, 2015). Pigments can have several advantages as colourants in such plastics, including: a) high brightness and good colour strength, b) improved fastness properties, and c) inhibition of polymer degradation (Christie, 1998).

The case study on automotive plastics simulates the decision context of a manufacturer who has to compare and select the most sustainable colour for plastic bumper of an Alfa Romeo MITO choosing among two hypothetical pigments: nano-sized organic pigment (n-OP) or nano-sized carbon black (n-CB). The n-OP comprises of nano-sized diketopyrrolopyrrole (DPP) pigments, ranging from 14 to 151 nm (median 43 nm), that are used to impart red colour (with the colour index being the Pigment Red 254). The n-CB comprises of nano-sized rubber grade pigments, ranging between 10 and 100 nm, which are used to impart black colour. The n-OP and n-CB pigments are used to colour plastics with a content of 0.2% and 1% in the polymer matrix, respectively.

2.2.2.2. Input information. The application of the HHRA methodology to the case study includes assessing HH risks for nano-sized carbon black (n-CB) and for nano-sized organic pigment (n-OP).

The first category of inputs required for the application of the RC methodology to n-CB is presented in Table 2, where the assessed HH risk scenarios and the related risk results are reported. In this case, no toxicological or exposure assessment experiments were conducted in the SUN project and HHRA was conducted for n-CB from literature data (see Supplementary information, Section 2, for details). The risk assessment included 4 exposure scenarios (one for each life cycle stage), i.e. one exposure scenario considering both inhalation and dermal contact for both workers and consumers in the use stage (ES3), and three exposure scenarios considering both inhalation and dermal contact for workers in the synthesis (ES1), formulation (ES2) and end of life (ES4) stages. This assessment identified one non-acceptable risk (i.e. occupational risk via inhalation in the production of n-CB, ES1) as reported in Table 2 (sixth column).

HHRA results obtained for n-OP are presented in detail in Pizzol et al. (2019) and are not reported in this paper because they showed acceptable risks for all the analysed exposure scenarios and therefore did not require the application of the RC methodology. More specifically, five exposure scenarios have been assessed: one for the synthesis stage (occupational risk via inhalation and dermal contact), one for the formulation stage (occupational risks via inhalation, dermal contact and inadvertent oral exposure), two for the use stage (consumers and workers exposure via inhalation and dermal contact) and one for end of life stage (occupational exposure via inhalation and dermal contact) (Pizzol et al., 2019).

To apply the RC methodology to the single non-acceptable risk in n-CB life cycle, available TARMMs relevant to the assessed exposure scenario were collected from industry and exposure assessment experts. For each of them, efficacy was derived by calculating the average of experts' approved literature values included in the TARMM database. This information is summarised in Table 2, at columns 7th and 8th. Similarly, costs of TARMMs used to control risks of n-CuO paint are described in Table 2, at columns 9th and 10th. Cost for containment was deemed difficult to estimate as it is inherently related to the production technology, while cost for the two types of LEV was available as ranges.

Table 1

Results from applying Technological Alternative and Risk Management Measures (TARMMs) to Human Health (HH) risks estimated for the CuO and $Cu_2(OH)_2CO_3$ case studies by Hristozov et al. (2018). Columns 1 to 6 report the results of the HHRA, while columns 7 to 10 report TARMMs' application, including efficacy and costs; column 11 reports the residual risks after a specific TARMM application; n.a. = not applicable. SYN, synthesis; FOR, formulation; USE, use; EoL, end of life.

Exposure scenario (ES)	**LUA**			**Exposure level (EXP_i)**	**HHRA results**	**TARMM application**				**Residual risk**
	LC stage	**Target**	**Exposure route**			**Relevant TARMM**	**Efficacy**	**TARMM Cost**	**Source**	
ES1: Laboratory scale CuO powder production, handling and packing	SYN	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES2: Pouring CuO nanoscale powder in the wood coating matrix	FOR	Worker	Inhalation	**assessed**	**93.33%**	Local exhaust ventilation	99.9%	Local Exhaust Ventilation (LEV, vertical/horizontal laminar flow hood) [1]: 3280 to 5818.	Expert elicitation	2.5%
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES3: Applying CuO wood coating to the substrate	USE	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES4: Sanding, cutting, drilling and sawing wood treated with CuO preservative	USE	Worker, Consumer	Inhalation	**assessed**	**99.9%[2]**	On-tool extraction FFP3 mask	90.0% 96.9%	On-tool extraction: 259. FFP3 mask: 5.	Expert elicitation Internet search	**31.10%**
		Worker, Consumer	Dermal, Perioral	**assessed**	**0.00%**	-	-	-	-	-
	EOL	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES5: Consumers transfer to skin from surfaces by rubbing	USE	Consumer	Dermal	negligible	negligible	-	-	-	-	-
ES6: $Cu_2(OH)_2CO_3$ powder production, handling and packing	SYN	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES7: Milling of $Cu_2(OH)_2CO_3$ slurry for the impregnation stock solution	FOR	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES8: Workers impregnating wood in an industrial setting	USE	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES9: Workers constructing garden fences, decking, cladding, playgrounds, vegetable gardens using the treated wood	USE	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES10: Consumer transfer to skin from surfaces by rubbing	USE	Consumer	Inhalation	negligible	negligible	-	-	-	-	-
		Consumer	Dermal	negligible	negligible	-	-	-	-	-
ES11: Children exposed directly to the treated wood by skin contact, transfer of copper to the mouth and related ingestion	USE	Consumer	Oral	**assessed**	**8.48%**	n.a.	-	-	-	-
ES12: Sanding, cutting, drilling and sawing wood treated with $Cu_2(OH)_2CO_3$ preservative	EOL	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES13: Leaching during contact with water and related potential human exposure (appl. to both CuO and $Cu_2(OH)_2CO_3$)	USE	Consumer	Oral	negligible	negligible	-	-	-	-	-
	EOL	Public	Oral	negligible	negligible	-	-	-	-	-

3. Results of case study application

3.1. Nano-scale CuO and $Cu_2(OH)_2CO_3$ used as antimicrobial and antifungal coatings and impregnations

The input data and the results of the case study on nano-scale CuO and $Cu_2(OH)2CO_3$ used as antimicrobial and antifungal coatings and impregnations are reported in Table 1.

Table 1, column 11th illustrates the residual risk after the application of the RC methodology to n-CuO based paint considering the application of TARMMs to the non-acceptable risks identified along the n-CuO paint life cycle. Accordingly, risks were reduced to acceptable levels in the formulation stage, but not in the use phase where on-tool extraction (Local exhaust ventilation (LEV)) with dust extraction through pumps and FFP3 masks were not successful in controlling risk due to sanding wood.

3.2. Nano-pigments colourant for plastic automotive part case study

The input data and the results of the case study on nano-pigments

Table 2

Results from applying Technological Alternative and Risk Management Measures (TARMMs) to Human Health (HH) risks estimated for the n-CB pigments used to colour plastics. Columns 1 to 6 report the results of the HHRA, while columns 7 to 10 report TARMMs' application, including efficacy and costs; column 11 reports the residual risks after a specific TARMM application; n.a. = not applicable. SYN, synthesis; FOR, formulation; USE, use; EoL, end of life.

Exposure scenario (ES)	LUA			Exposure level (EXP_i)	HHRA results	TARMM application				Residual risk
	LC stage	Target	Exposure route			Relevant TARMM	Efficacy	TARMM Cost	Source	
ES1: Production of n-CB	SYN	Worker	Inhalation	**assessed**	**25.2%**	Containment (pyrolysis ovens)	0.9	Difficult to estimate	Expert elicitation	2.0%
						LEV (Horizontal/downward laminar flow booth and Other enclosing hoods)	0.9	range from 3280 to 5818	Expert elicitation	2.0%
						LEV (Movable capturing hoods)	0.5	range from 890 to 2676	Expert elicitation	**14.0%**
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES2: Manufacture of Master-batch containing 1 wt.% n-CB	FOR	Worker	Inhalation	negligible	negligible	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-
ES3: Consumers handling and working with PP-CB performing operations such as sawing, sanding or drilling that might lead to release of airborne particles.	USE	Worker, Consumer	Inhalation	**assessed**	0.0%	-	-	-	-	-
		Worker, Consumer	Dermal	negligible	negligible	-	-	-	-	-
ES4: Shredding	EOL	Worker	Inhalation	**assessed**	0.0%	-	-	-	-	-
		Worker	Dermal	negligible	negligible	-	-	-	-	-

colourant for plastic automotive part case study are reported in Table 2.

Table 2, column 11 illustrates the residual risk after the application of the RC methodology to n-CB along the life cycle stage.

Out of the three TARMMs considered in Table 2, containment and LEV (Horizontal/downward laminar flow booth and Other enclosing hoods) are successful in reducing risks to acceptable levels. As containment can be considered as a suitable option only if it is planned in the earlier phases of the production process building, its costs cannot be easily determined and compared to LEV. It is likely that if industries are not willing to modify their production technology, LEV (Horizontal/downward laminar flow booth and Other enclosing hoods) will be chosen for risk control.

4. Discussion

This paper described a quantitative methodology implementing risk control measures through the life cycle of NEPs, which has significant practical value for industries. The development of the RC methodology was based on the guidance documents provided for the implementation of Chemical Safety Assessment (CSA) according to the EU REACH regulation. Therefore, the proposed methodology is particularly relevant for SMEs as it will enable them to easily perform regulatory safety assessment and to make risk management decisions. This can reduce their R&D&I costs to enable them to more effectively compete with larger industries. Moreover, implementation of best practice RC can reduce the uncertainty regarding the risks from nanotechnology in the early stages of innovation by working in tandem with evolving regulation.

The RC methodology for NEPs proposed in this paper has some limitations. One, there is uncertainty in efficacy and cost data used in the case study application. Limited data on TARMMs efficacy is available and expert judgement was used to filter out the most relevant and reliable data, which was averaged to obtain a single value for efficacy. The range of available data is vast and it is possible that further studies may provide more accurate or context specific measurements for TARMMs efficacy. In the case of cost information, cost ranges are usually available instead of single values. Despite this important limitation, in the case of TARMMs with large differences in efficacy and cost, important insights can still be gained.

In our approach, uncertainty is addressed through inclusion of probabilistic risk assessment (RA) as well as best practices for RA. In contrast to the deterministic RA, the probabilistic RA described in Hristozov et al. (2018) and Pizzol et al. (2019) allows clear assessment and communication of the sources of uncertainty in the estimated risks. This in turn guides what kind of additional data needs to be generated and in which exposure scenarios more precautionary risk control measures may need to be adopted. This information is useful as it can support industries in optimising the cost allocated to risk management.

To demonstrate the RC methodology, it was applied to case studies representing real industrial products: nano-scale copper oxide and basic copper carbonate used as antimicrobial and antifungal coatings and impregnations and two nano pigments (organic pigment and carbon black) used to colour plastic automotive parts. While not all human health risks could be mitigated in these case studies, some risks could be controlled to fall to acceptable levels (ES2 in Table 1 for n-CuO and ES1in Table 2 for n-CB). In the case of the nano-related risks due to sanding and sawing n-CuO painted wood in the use phase (ES4 in Table 1), the application of on-tool extraction and FFP3 masks did not effectively reduced the estimated risks to acceptable levels. Considering that these risks were estimated based on conservative exposure estimations provided by available exposure models, accurate exposure measurements in occupational settings will probably modify the risk assessment results toward acceptable levels. In this case, the costs to monitor exposure in occupational settings in order to assess more accurate site-specific risks should be compared with the cost of implementing more expensive TARMMs able reduce the risks to acceptable levels, if available.

5. Conclusion

The complexity of NEPs and their regulatory requirements reflects a profound need to assist nanotechnology industries in assessing occupational and consumer risks and in selecting sound risk control options to manage possible non acceptable health risks in accordance with legal requirements.

In this paper we propose a quantitative methodology for selecting the optimal risk control strategy based on information about human health and ecological risks, efficacy of risk mitigation measures, cost and other contextual factors. Such methodology includes uncertainty assessment (by including probabilistic RA) and was applied to two real industrial NEPs to demonstrate its strengths in supporting the decision making process in controlling human health risks along the life cycle of innovative products.

This is illustrated in the n-CuO paint case study, where Local Exhaust Ventilation is used to control risks due to inhalation during pouring CuO nanoscale powder, while the combination of on-tool extraction and FFP3 masks was applied to reduce inhalation risks due to sanding painted wood (although in the latter case the residual risks were still non-acceptable). In the nano-pigments case study, the application of three TARMMs (Containment (pyrolysis ovens), LEV (Horizontal/downward laminar flow booth and Other enclosing hoods) and LEV (Movable capturing hoods)) were compared to estimate the residual risk posed by the inhalation of n-CB pigment during its synthesis. Out of the three TARMMs, the first two alternatives were successful in reducing risks to acceptable levels. For the selection of the most suitable TARMM to be used, complementary information related to associated costs and TARMMs implementation timing (e.g. only during the production process design and construction or, later, during the operational phases) need to be accounted. As containment should be planned during the first stages of the production process design and construction, its costs cannot be easily determined and compared to LEV. It is likely that if industries are not willing to modify their production technology, LEV (Horizontal/downward laminar flow booth and Other enclosing hoods) will be chosen for risk control.

Finally, the proposed RC methodology should not be considered as restricted to NEPs only but can be extended to the assessment of innovative chemical products across various application domains. The inclusion of additional information (i.e. not specific to nano-sized materials) in the TARMM database will be the only requirement needed for using the RC module in other application contexts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.06.011.

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