RESEARCH ARTICLE

A methodology on how to create a real-life relevant risk profile for a given nanomaterial

With large amounts of nanotoxicology studies delivering contradicting results and a complex, moving regulatory framework, potential risks surrounding nanotechnology appear complex and confusing. Many researchers and workers in different sectors are dealing with nanomaterials on a day-to-day basis, and have a requirement to define their assessment/management needs. This paper describes an industry-tailored strategy for risk assessment of nanomaterials and nano-enabled products, which builds on recent research outcomes. The approach focuses on the creation of a risk profile for a given nanomaterial (e.g., determine which materials and/or process operation pose greater risk, where these risks occur in the lifecycle, and the impact of these risks on society), using state-of-the-art safety assessment approaches/tools (ECETOC TRA, Stoffenmanager Nano and ISO/TS 12901-2:2014). The developed nanosafety strategy takes into account cross-sectoral industrial needs and includes (i) Information Gathering: Identification of nanomaterials and hazards by a demand-driven questionnaire and on-site company visits in the context of human and ecosystem exposures, considering all companies/parties/downstream users involved along the value chain; (ii) Hazard Assessment: Collection of all relevant and available information on the intrinsic properties of the substance (e.g., peer reviewed (eco)toxicological data, material safety data sheets), as well as identification of actual recommendations and benchmark limits for the different nano-objects in the scope of this projects; (iii) Exposure Assessment: Definition of industry-specific and application-specific exposure scenarios taking into account operational conditions and risk management measures; (iv) Risk Characterisation: Classification of the risk potential by making use of exposure estimation models (i.e., comparing estimated exposure levels with threshold levels); (v) Refined Risk Characterisation and Exposure Monitoring: Selection of individual exposure scenarios for exposure monitoring following the OECD Harmonized Tiered Approach to refine risk assessment; (vi) Risk Mitigation Strategies: Development of risk mitigation actions focusing on risk prevention.

By Christa Schimpel, Susanne Resch, Guillaume Flament, David Carlander, Celina Vaquero, Izaskun Bustero, Andreas Falk

INTRODUCTION

In the last decade, nanotechnology entered the policy arena as a technology that is simultaneously threatening and promising.[1] The combination of size, structure and physical/chemical properties of nanomaterials (NMs) offer remarkable technological advances and innovations but may also entail new risks for human health and the environment.[2–4] Thus, an appropriate management of nano-related risks have been identified by the EU Commission as a vital empowering issue for the success of NMs and nanotechnologies.[5] One bottleneck that hinders the safe and sustainable development of nano-innovations in various industrial sectors is that nano-specific legislative

Christa Schimpel *is affiliated with the BioNanoNet Forschungsgesellschaft mbH, Graz, Austria (E-mail address: christa.schimpel@bionanonet.at).*

Susanne Resch *is affiliated with the BioNanoNet Forschungsgesellschaft mbH, Graz, Austria.*

Guillaume Flament *is affiliated with the Nanotechnology Industries Association, Brussels, Belgium.*

David Carlander *is affiliated with the Nanotechnology Industries Association, Brussels, Belgium.*

Celina Vaquero *is affiliated with the Tecnalia Research & Innovation, Miñano, Spain.*

Izaskun Bustero *is affiliated with the Tecnalia Research & Innovation, Miñano, Spain.*

1871-5532
http://dx.doi.org/10.1016/j.jchas.2017.06.002

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

measures at the EU level are currently vague; while a decade of research in nanotoxicology has failed to identify specific modes of action for nanomaterial toxicity,[6] the regulatory framework has been growing disorderly, creating an uncertain environment for industry.[7,8]

In the European Union, NMs are considered as a chemical substance and therefore fall in the existing regulatory framework of regulation 1907/2006[1] concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Since REACH does not explicitly integrate provisions regarding NMs, they are bound to registration like other substances. Since February 2012, registrants can voluntarily declare that their substance is in "nanomaterial form" and with the Second Regulatory Review on NMs produced by the Commission in the same year, the regulator promised improvements to the registration of such substances under REACH, including potential amendments of the Regulation's annexes. This process is currently under progress, but will not be ready for the 2018 registration deadline for substances manufactured or imported in amounts exceeding one ton a year as a two-year standstill period applies.

In addition, several pieces of sectoral European regulation directly target NMs and nanotechnology (e.g., food and novel foods, cosmetics, biocides, electronic waste, etc.). To support a harmonized understanding of what constitutes a nanomaterial, the European Commission has published a Recommendation for a Definition of a nanomaterial (696/2011)[2] which defines a nanomaterial as follows:

'2. 'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.'

While this definition has been taken up in most of the European and national legislation tackling NMs, there remains a variety of definitions (e.g. NMs for food, etc.). A review of this definition is also currently at work by the European Commission. Regulatory measures specific to NMs range from labelling requirements to additional testing and pre-market authorisation.

On top of this EU Framework, some EU Member States, including France, Belgium, Denmark and Sweden, have developed nanomaterial registers which condition the manufacturing, importation and distribution of NMs to their prior registration in a national database.

As a consequence, researchers are unsure how to work safely with NMs. Industry dealing with NMs has to cope with an unstable and unreliable framework to develop safe and legally compliant products, and consumer and public confidence of emerging nano-innovations may severely be affected.[9]

Another problem is that reliable toxicity information and data on the levels of NMs that the worker, consumer and environment may become exposed to are either limited or non-existent. Without such data, it is difficult to quantify exposures and it becomes even more difficult to effectively respond to any potential nano-related risks.[10,11]

Although relatively limited data are available, the fact remains that NMs and/or nano-enabled products may pose a risk depending on their potential hazard and exposure properties. Nonetheless, it cannot be concluded that nano-related risks are higher compared to conventional materials/bulk counterparts. Still, a strategic framework that can properly define the nature of nano-related risks is needed.[12–14]

According to legislation and the current knowledge, NMs have to be treated the same way as chemical substances, which means the standard information requirements and the Chemical Safety Assessment (CSA) described in the Annexes VII–X of the REACH regulation shall be applied. Quantitative risk estimation represents the most important feature of a CSA. Under REACH, risk estimation/characterisation is defined as the comparison of exposure levels and hazard levels leading to the calculation of a Risk Characterization Ratio (RCR). However, in the case of NMs quantitative risk assessment is not feasible due to the fact that presently neither agreed standardised, validated and specific methods for measuring personal exposure (i.e., breathing zone measurements) to engineered NMs are available nor are there validated models providing quantitative estimates of human (worker and consumer) or environmental exposure.[15] The technical limitations of currently available sampling and analytical methods may also raise issues and might not propose sufficient sensitivity to properly assess very low exposure levels.[16] The best available guidance for exposure measurement suggests that in addition to an appropriate characterisation of particle size distribution, measurements should at least encompass an assessment of mass, but where possible also include number and/or surface area concentration.[17,18]

Confronted with these limitations, it was decided that the most sensible course of action is to focus on (i) qualitative risk assessment covering all

[1] EC, 2006. Regulation (EC) 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L; http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20140410&from=EN.

[2] European Commission 2011 (2011/696/EU). Commission recommendation on the definition of nanomaterial. OJ L 275/38, 18 October 2011.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

stages of the lifecycle, (ii) hazard/risk avoidance rather than address them as an exposure (exercising an appropriate level of precaution) and (iii) strong involvement of industry, risk managers and relevant stakeholders.

In addition, input from (i) experts in the NanoSafety Cluster (NSC) community, (ii) EU institutions (e.g., ECHA), (iii) international organisations (e.g., OECD[27]), (iv) industry initiatives (e.g., ECETOC[28,29]), (v) European Center for Nanotoxicology (EURO-NanoTox),[54] and (vi) peer-reviewed scientific literature, have been considered to ensure consistency at EU level and alignment to the state-of-the-art.

In this framework, hazard/exposure potentials are measured on scales called "bands" using the control banding approaches Stoffenmanager Nano[19] and ISO/TS 12901-2:2014.[20] Additionally, risk values were calculated via computational risk screening model ECETOC TRA.[21]

FRAMEWORK FOR DEVELOPING A RISK PROFILE

In brief, the proposed nanosafety concept was developed by linking the strategies of hazard assessment, life cycle assessment, and risk analysis within the same toolbox. First, all available information and data on physicochemical properties, exposure, toxicokinetics, fate, and hazard of given NMs is collected to build general exposure scenarios (case studies) throughout the whole life cycle of the NMs. Next, initial exposure estimates are obtained on a PROC (process category)-specific basis. For each PROC, exposure values are calculated according to the selected/assigned PROC-class as well as several parameters such as the frequency and duration of exposure, the presence of a local exhaust ventilation (LEV), etc. The final output is a library of critical hotspots associated with initial exposure estimates, which are universally applicable across diverse industrial and consumer sectors. This may help to develop mitigation plans designed to manage, eliminate, or reduce risk to an acceptable level and thus lowering the commercialisation barrier for innovative nanotechnology driven products.

The proposed concept is currently used for the safety assessment in two H2020 pilot line projects (INSPIRED and Hi-Response) dealing with high throughput synthesis and scale-up of NMs for printed electronic applications. The following sections ("Information gathering" to "Refined risk characterisation and exposure monitoring") describe in more detail the actions to be considered when ensuring the responsible development of NMs and nano-enabled products (taking into account the whole innovation life cycle; i.e.; cradle-to-grave analysis) from an occupational and environmental safety and health perspective.

Applicable Regulatory Framework

In this context, the NMs used are subject to a series of European regulations where their size may trigger additional requirements. Because they are chemical substances, NMs fall under general term of "substance" in REACH and are classified according to Regulation on classification, labelling and packaging (CLP).[3] Discussions towards the modification of REACH annexes to introduce the term "nanoform", and requirements to provide information on the size, shape and surface modification of individual nanoforms, are ongoing and will eventually apply to European nanomaterial manufacturers and importers.

Under REACH, the responsibility falls on the registrant to assess the hazards of the substance in the registration dossier. In other instances, regulations give the role of substance evaluation to European authorities and make use of positive lists of authorized substances (e.g. food, food contact materials). When used in electronics, NMs also need to comply with the Waste Electrical and Electronic Equipment Directive (WEEE) – 2012/19/EU[4] and the Directive on the Restriction of the use of Certain Hazardous Substances in Electrical and Electronic Equipment (RoHS2) – 2011/65/EU.[5] In the WEEE directive from 2012, the legislator referred to the 2009 Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on 'Risk assessment of Products of Nanotechnologies'[22] which considers that 'when nanomaterials are firmly embedded in large structures, for example in electronic circuits, they are less likely to escape this structure and no human or environmental exposure is likely to occur.' Article 8(2) of the Directive nevertheless states: 'the Commission is invited to evaluate whether amendments to Annex VII are necessary to address nanomaterials contained in EEE.' At the moment, no action has been taken to amend Annex VII – Selective treatment for materials and components of waste electrical and electronic equipment for nanomaterials.

RoHS2 sets restrictions for the use of hazardous materials in electrical and electronic equipment. The directive suggests that NMs should be considered when reviewing Annex II – List of Restricted Substances. In 2012–2014, the Environment Agency Austria (Umweltbundesamt) wrote the methodology for the review of the List of Restricted Substances under RoHS2.[23] The methodology does not prioritise NMs among other materials, but suggests caution in the assessment of such substances.

[3] Regulation 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directive 67/548/EEC and 1999/45/EC and amending Regulation (EC) No 1907/2006

[4] Directive 2012/19/EU of the European Parliament and of the Council of 4 July 2012 on waste electrical and electronic equipment (WEEE); http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32012L0019.

[5] Directive 2011/65/EU of the European Parliament end of the Council on the Restriction of the use of Certain Hazardous Substances in Electrical and Electronic Equipment (RoHS2); http://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32011L0065.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

Information Gathering

Effective risk assessment and management both assume a high degree of information disclosure. In order to focus on the risk assessment, stakeholders, especially employees as well as health and safety representatives in the risk assessment are actively involved. The employees have a good understanding of their area of work and the risks involved, so they are entitled to an opinion on how safety systems of work are designed, developed, monitored and assessed.

The information gathering process is split up in two individual steps. The starting point is the collection of general information, which are important with regard to nanosafety via a questionnaire survey (see Section "Questionnaire survey" and Supplementary information). In the second step, companies are visited to gain deep and detailed insight into real working conditions on-site (see Section "Company visits" and Supplementary information).

Questionnaire survey

A detailed questionnaire (see Supplementary information) is shared with technical experts and/or safety representatives in order to identify all materials, processes, products and applications, which may be relevant in terms of nanosafety. More precisely, this initial assessment involves identifying the potential source(s) of manufactured NMs emissions by reviewing the type of process, process flow, material inputs and discharges, and work practices.

The elaborated safety strategy is based on these case-by-case surveys, addressing the specific requirements of the involved parties (i.e., data on the characteristics of the NMs, as well as contextual information on the operative conditions and risk controls applied). The filled-in questionnaires will be evaluated and uncertainties are going to be clarified.

Company visits

Analysis of the filled-in survey is complemented by in-depth interviews at the sites and/or face-to-face meetings with industrial partners to get an extensive impression of the on-site working conditions. The visits also include a guided tour through the lab facilities, discussions with technical developers, production experts as well as health and safety managers. It is a valuable way of involving the staff who do the work. They know the risks involved and scope for potentially dangerous shortcuts and problems. Employees are more likely to understand why procedures are put in place to control risks and follow them if they have been involved in developing health and safety practices in their workplace.

As a next step, the companies are asked to fill in a template to itemise the processes into every single process step (see Supplementary information).

Hazard Assessment

Hazard assessment encompasses the collection of all relevant and available information on the intrinsic properties of the substance that may support the identification of hazardous properties and critical effects.[24]

Thus, the collection of hazard data includes information related to: (i) Physicochemical properties (e.g., physical form, vapour pressure, dustiness, solubility, nanomaterial concentration) provided by material safety data sheets (MSDS), registration dossiers for REACH; (ii) (Eco)toxicological outcomes (e.g., acute and chronic systemic effects, genotoxicity, irritation) provided by case studies and/or peer reviewed publications, internal reports regarding health and safety of NMs; (iii) Occupational and environmental benchmark/threshold limits (i.e., Predicted no effect concentration (PNEC): Concentration of the substance below which adverse effects in the environmental sphere of concern are not expected to occur; Derived No-Effect Level (DNEL): Level of exposure to a substance above which humans should not be exposed).

Particularly, the above-mentioned exposure limit values are crucial, as they represent the reference values for assessing whether risks are controlled. A risk score (i.e., risk characterisation ratio) is then calculated via comparing measured or estimated exposure levels and the PNECs for the environment and DNELs for human health.[25]

Exposure Assessment

The objective of the exposure assessment phase is to identify exposure scenarios along the NMs lifecycle. Under REACH, exposure scenarios cover manufacturing, all identified uses of a substance and all risks related to consumers, workers and the environment arising from such uses, considering the use of the substance on its own, in mixtures or in an articles as defined by the identified uses.[26]

In order to cover as much of the spectrum of likely releases as possible, usually more than one scenario need to be developed and modelled – representing e.g., low, mean (i.e., realistic), and high release factors. Taken together, these various scenarios can cover then the entire value chain spectrum of possible releases (and environmental concentrations) – and the related environmental impacts taken into account operational conditions and necessary risk management measures.

The exposure scenario mapping plays a fundamental role within the safety assessment, since it constitutes the basis for the exposure estimation and risk characterisation.[26]

Risk Characterisation

In order to prioritise previously identified exposure scenarios, the first Tier tool ECETOC TRA (=Targeted Risk Assessment) is used. ECETOC TRA was selected as a result of extensive literature research and discussions with experts from NANoREG. The integrated tool enables an assessment of both occupational and environmental exposure scenarios. The model is based on a relation between PROCs/ERCs (process categories/environmental release categories described in the REACH guidance[27]) and basic exposure threshold values. In particular, the software calculates whether the potential for exposure in a specific scenario is high or low.[21,28,29] However, it has to be considered that with respect to nanomaterial exposures, ECETOC TRA is able to give an indication of exposure levels. Since ECETOC was not initially designed to specifically assess nanomaterial exposure situations, the risk estimates may be inaccurate due to the limitations of the model.[30]

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

The tool requires the user to input some basic information on the substance (molecular weight, vapour pressure, substance form). The user can then select scenarios, as PROCs/ERCs, which pre-define the point of departure exposure value. A range of exposure modifiers are applied to establish the set of operational conditions and risk management measures that appear in the final scenario (see Supplementary information).

The output of ECETOC TRA is a simple description of type and basic conditions of use which can then be translated into calculated risk values via comparison of estimated data with indicative reference values (DNEL, OEL (occupational exposure limit), i.e., maximum admissible concentration at workplace, PNEC).

For each exposure scenario, the software calculates different risk characterisation ratios (RCR) according to Eq. (1). To assess worker's exposure, short-term and long-term inhalative as well as dermal RCRs are calculated. In addition, a RCR for long term total exposure is generated.

For environmental exposure assessment, a separate RCR for each environmental compartment is generated, i.e., marine water, freshwater, soil and sediment.

$$\text{RCR human (occupational) health} = \frac{\text{exposure}}{\text{DNEL}} \quad \text{RCR environment} = \frac{\text{PEC}}{\text{PNEC}} \tag{1}$$

A RCR value >1 indicates that there is risk in place for human health or the environment, while a value <1 means that no risk is present under the selected conditions.

Ideally, the exposure assessment should be based on quantitative measurements of the levels of the exposure, however, in practice, the availability of reliable exposure data is scarce and mostly limited to the workplace. Use of single tool estimates is unlikely to be persuasive enough for appropriate risk assessment. Hence, it has been recommended to use different methods for different risk-based decision contexts.[30,31] Therefore, semi-quantitative assessment via ECETOC TRA is supported by qualitative assessment using control banding tools (i.e., Stoffenmanager Nano and ISO/TS 12901-2:2014) to evaluate, if risks are adequately controlled in each pre-defined exposure scenario.

Control banding tools represent an alternative approach for risk assessment that can be used to identify and recommend exposure control measures to potentially hazardous substances with unknown or limited toxicological properties and for which there is a lack of quantitative exposure estimations. Control banding tools define hazard bands and exposure bands and combine these in a two-dimensional matrix, resulting in a score for risk control (proactive approach). Hazard banding consists in assigning a hazard band to a substance on the basis of a comprehensive evaluation of all available data on this material (often from a Material Safety Data Sheet, MSDS), taking into account parameters such as toxicity, and factors influencing the ability of particles to reach and/or deposit in the respiratory tract. (i.e., physical and chemical properties such as surface area, surface chemistry, shape, particle size). Following the hazard banding process, the second step is intended to determine an expected level of workers exposure which is designated as an exposure band. Matching the hazard band and the exposure band through a control banding matrix determines the appropriate level of control i.e. the control band. The greater the potential for harm and exposure, the greater the steps needed for control.[32,33]

The ISO/TS 12901-1[34] control banding approach allocates five bands for hazard, four bands for exposure and five risk level control bands. Once the hazard and exposure band are determined, a control measure strategy is suggested. This means that a substance with greater health hazards and higher exposure potential will have more stringent controls than a substance with low health hazards.

Stoffenmanager Nano applies five hazard bands, four exposure bands (emission potential) and three control bands for risk. The control bands (levels) are derived by combinations of the hazard and exposure bands in a two-dimensional decision matrix. Each control band (risk level) is associated with general recommendations for risk management and action that should be taken into consideration.[35,36]

Refined Risk Characterisation and Exposure Monitoring

When risk cannot reasonably be excluded via qualitative and semi-quantitative risk assessment, refined risk assessment becomes necessary (i.e., additional estimation based on higher tier estimation models, generation of measured exposure data).

Field-based, real-time workplace release and exposure measurements will be performed according to the OECD.[37] The proposed approach can be split into three tiers: At Tier 1 a decision has to be made, whether or not a release of nanoscale aerosols from NMs into workplace air can be reasonably excluded. If this is not the case, a basic exposure or release assessment is conducted utilizing easy-to-use, portable equipment/handheld devices for direct reading measurements (on-line) in Tier 2. Total particle concentration (TPC) is measured during the nano-related tasks and is compared with background concentration; if the comparison shows a significant increase in TPC, then a potential release of NMs due to the task may happen and a Tier 3 is suggested. Tier 3 is an expert assessment where the use of advanced on-line devices and the collection of samples for off-line analysis are simultaneously combined.

Risk Management and Strategies for Risk Mitigation

The main objective of this step is considering and incorporating safety measures of potential health (workers and envisaged users) and environmental safety concerns from the very beginning/at earliest stage in the innovation process and where necessary adapting the process and/or product design so as to create safer outcomes. Thus, risk mitigation actions focus on hazard/risk avoidance rather than address them as an exposure (i.e., Safe-by-Design).

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

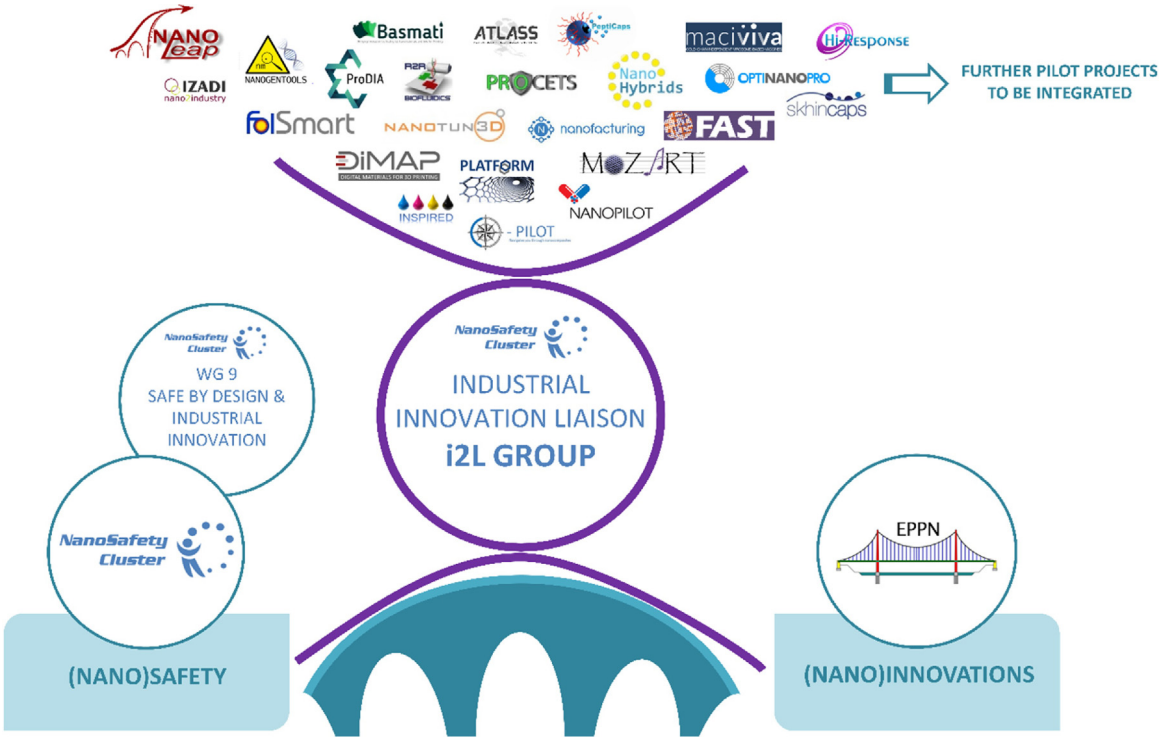

Figure 1. Linkage of NanoSafety Cluster, European Pilot Production Network (EPPN) and projects contributing to the i2L group.

RESULTS AND DISCUSSION

Recommendations of the Organisation for Economic Co-operation and Development (OECD) for a responsible strategy that aims to enable the safe development and use of NMs and nanotechnology include the proposal of integrating risk assessment of chemicals at all stages of the life cycle of a nanotechnology-based product.[38] Within the European Parliament and Council Regulation (EC) No 1907/2006 (REACH), risk assessment and risk characterisation is conducted under the overall framework of the chemical safety assessment (CSA) process[39] which basically encompasses three steps:

1. Hazard Assessment: The hazard assessment involves the analysis of available data on (eco)toxicological effects with respect to human health and the environment;
2. Exposure Assessment: The exposure assessment formulates exposure scenarios describing how a chemical is used by workers or consumers or how it is released into the environment (bearing in mind operational conditions and necessary risk management measures); and,
3. Risk Characterisation: The risk characterisation combines hazard and exposure to estimate risk; risk levels are defined via comparing of estimated exposure levels with threshold/benchmark exposure limits.

In order to create a holistic and cross-sectorial approach for the nano-related safety assessment, the concept is basically grounded on the classical framework[40] but has been modified – now covering six steps:

1. Information Gathering;
2. Hazard Assessment;
3. Exposure Assessment;
4. Risk Characterisation;
5. Refined Risk Characterisation and Exposure Monitoring and
6. Risk Management and Strategies for Risk Mitigation.

In addition, the development of the proposed safety framework also incorporates partnership and coordination between nanosafety experts, industries and other stakeholder groups. One crucial step forward to better link safety work and industry in ongoing projects was the establishment of the NanoSafety Cluster sub-group "industrial innovation liaison (i2L)",[6] founded in September 2016 in Paris. In brief, this group aims to maximise the synergies between ongoing nanosafety research and industry-oriented projects to identify possible cross-over safety strategies/guidelines valid for different sectors/markets, and to share "case study" experiences, including evaluation of which methodologies/guidelines are most useful and which knowledge gaps/limitations exist. Additionally, this group will support technical development in the European Pilot Production Network (EPPN) (see Figure 1).

There have been a number of complementary approaches proposed to evaluate the potential risks and/or serve as decision support tools for NMs/nano-enabled products.[41] In order to assess the advantages and limitations of existing RA frameworks

[6] http://www.nanosafetycluster.eu/working-groups/industrial-innovation-liaison-i2l-wg10.html.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

and tools, as a first step we conducted an extensive literature survey to collect information from completed and ongoing European research projects or by other international organisations and committees to ensure consistency at EU level and alignment to the state-of-the-art.

The most important sources of knowledge from relevant research projects (including the most recent and relevant publications and nanoEHS tools) are outlined in Table 1.

As indicated in the table above, several approaches exist for risk estimation; however, none of these concepts represent a seamless strategy to effectively manage the multidisciplinary nature of nanotechnology and their related risks. Carrying out risk assessment is strongly depended on information and data availability (e.g., nano-specific exposure data/limits).[28] Taking into account that recently a wide variety of NMs (e.g., raw materials, intermediate components) and nanotechnology-enabled consumer products are in the pipeline, we do not have the luxury to investigate every aspect of nanomaterial toxicity.[53] Nanotechnology is reality now. Responding to this challenge, we decided to focus on immediate safety measures. Thus, the main goal of our safety concept is the development of an instant plan/safety strategy for industry workers which are handling NMs by a day-to-day basis. The primary objective is to protect human health as well as the environment even in the absence of complete information, without stifling innovation. As indicated in Figure 2, the proposed safety concept follows the general REACH (CSA) approach applied to chemicals but is strongly moving towards a joint application of risk/safety assessment and life cycle assessment. Moreover, a strong focus is placed on "objective research" which suggests that the nature of the risk can be properly defined by making best usage of available data and involvement of highly renowned players in the research and industrial field and other stakeholders (e.g., active bodies in regulation/standardization). Combining collected

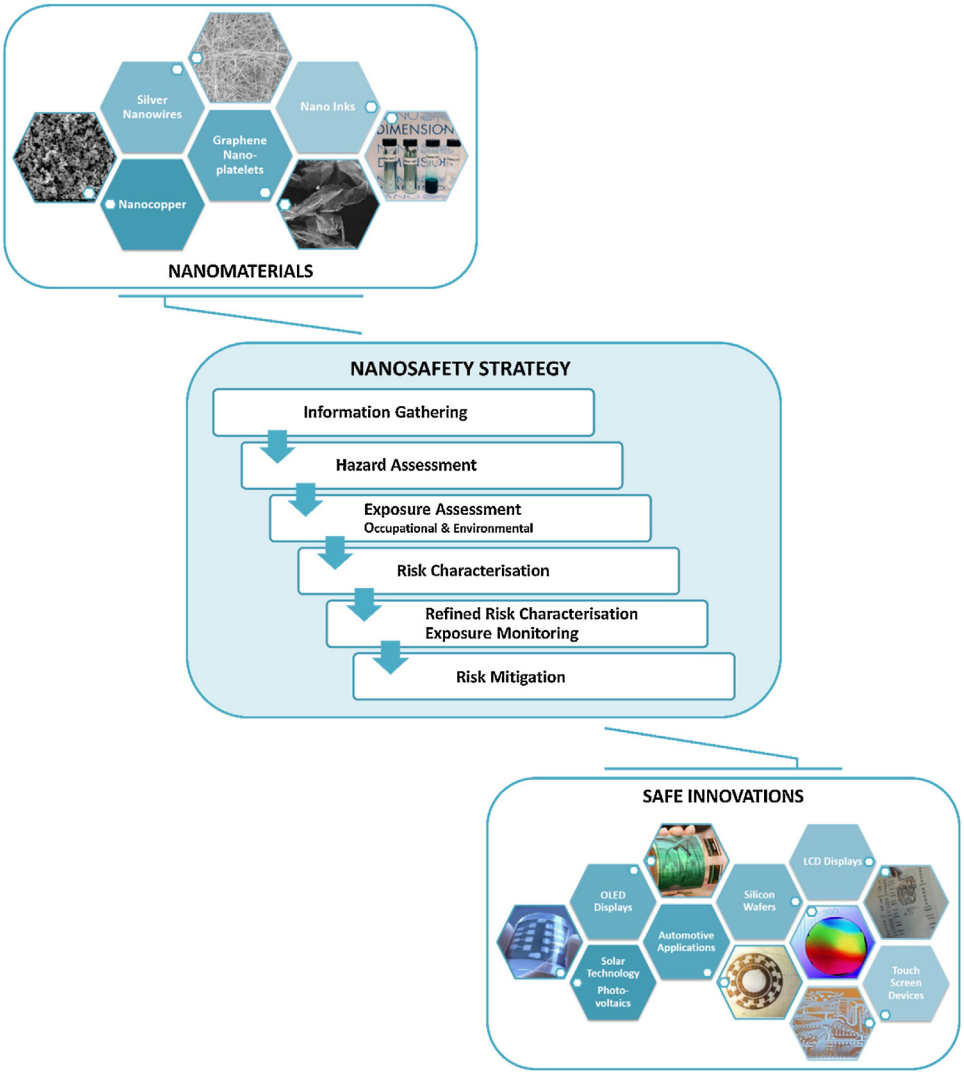

Figure 2. Overview of the different phases of the suggested nanosafety concept.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

Table 1. Selection of State-of-the-Art RA Frameworks and Tools (in Alphabetical Order).

Framework	Reference
GuideNano	http://www.guidenano.eu/
ITSnano	Stone et al.[42]
LICARA	Som et al.[43]
MARINA Framework	Bos et al.[44]; http://www.marina-fp7.eu/
NANEX/MARINA	Sikorová et al.[45]; http://www.nanex-project.eu/
NanoValid	http://www.nanovalid.eu/
REACHnano	http://www.lifereachnano.eu/
RIP-oN 3 Report	Aitken et al.[17]
Scaffold	http://scaffold.eu-vri.eu/
SUN	Malsch et al.[46]; http://www.sun-fp7.eu/
Tools	**Reference**
ANSES Tool	Brouwer[33]
ConsExpo	Bremmer et al.[47]
Control Banding Tool (ISO/TS 12901-2:2014)	ISO[34]
ECETOC TRA Tool	ECETOC[21]
GuideNano Tool	http://www.guidenano.eu/
LICARA NanoScan	Van Harmelen et al.[48]
NanoRiskCat	Hansen et al.[49]
NanoSafer	Jensen et al.[50]
REACHnano ToolKit	REACHnano Consortium[28]
SimpleBox4Nano	Meesters et al.[51]
Stoffenmanager Nano	Van Duuren-Stuurman et al.[19]
Swiss Precautionary Matrix	Hoeck et al.[52]

hazard data with identified exposure scenarios (i.e., exposure assessment step) the result obtained is a library of critical hotspots associated with initial exposure estimates (i.e., risk characterisation/prioritisation stage).

For the calculation of risk values and definition of the likelihood of release, three tools were selected for qualitative and semi-quantitative risk assessment respectively. General descriptions/background information related to the tools, the selection criteria and obtained results are outlined in Table 2.

As long as data and exposure limits for NMs are not available, quantitative risk assessment is not feasible. Thus, as a starting point we established an immediate safety concept based on qualitative risk assessment via the ISO/TS 12901-2:2014 Control Banding Tool and the Stoffenmanager Nano Tool on the one hand, and semi-quantitative risk assessment using ECTEOC TRA on the other. In the future, however, the objective is shifting priorities over time from a safety strategy compliant with the current provisions of REACH to an effective and sustainable safety concept which allows nano-specific quantitative exposure estimation (built on nano-specific exposure limits and measurement principles) and which will adapt to the future evolutions of REACH annexes regarding NMs (see Figure 3).

In summary, the proposed approach is based on the current state of knowledge and is flexible enough to identify critical hotspots along the innovation chain/life cycle associated with initial exposure estimates. However, further elaboration and refinement is crucially needed. Furthermore, the approach can also be used to identify those situations/processes where the use of nano-specific read-across, grouping, and (Q)SAR is likely to become realistic in the

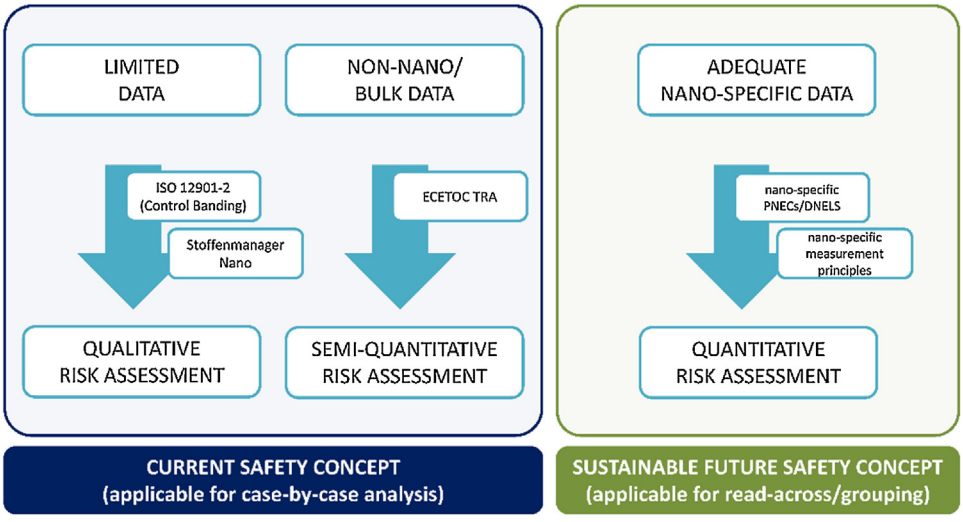

Figure 3. Current vs future safety concept.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

Table 2. Overview of Selected Risk Assessment Tools Included in the Nanosafety Concept.

	Qualitative Risk Assessment Tools		Semi-Quantitative Risk Assessment Tool
Name	ISO/TS 12901-2:2014 (Control Banding)[34,54]	Stoffenmanager Nano (Control Banding)[19,35]	ECETOC TRA (Targeted Risk Assessment) Tool[55]
Description	- Approach addressing likelihood of release, based on limited amount of information		- Approach for calculating risk values via comparison of estimated data with indicative reference values, based on mandatory inputs related to physicho-chemical properties, operational settings, RMM
	- Hazard/exposure potentials are measured on scales called "bands" ◦ Bands are typically plotted on a two-dimensional matrix, which results in establishing a control band (ISO) or a risk band (Stoffenmanager Nano) ◦ Risk control is achieved through recommendations of appropriate risk management measures (RMM) (e.g., engineering and administrative controls) as well as personal protective equipment (PPE)		
General Structure	- Information gathering		- Information gathering
	- Assignment of nanomaterial to a Hazard Band → hazard banding		- Definition of exposure scenarios (taking into account operational conditions, RMM)
	- Description of potential exposure characteristics → exposure banding		- Assignment of scenarios to a PROCs/ERCs (process categories/environmental release categories described in the REACH guidance)
	- Definition of recommended work environments and handling practises → control banding		- Final output is a library of critical hotspots associated with initial exposure estimates
	- Evaluation of the control strategy (action plan) based on the chosen scenario		
Output	- Hazard band (HB) - Exposure Band (EB) - Control Band (CB)	- Hazard band (HB) - Exposure Band (EB) - Risk Band (RB)	- Risk characterisation ratio (RCR)
Selection Criterion	✔ Standardised ISO-guideline	✔ Real case study tested (e.g., EU-funded project SCAFFOLD)	✔ Real case study tested (e.g., EU-funded project NANoREG)[56]
	✔ Usable in the absence of exposure and benchmark limits	✔ Nano-specifity	✔ Compliant with REACH regulation (i.e., using the ECHA use descriptor system)
		✔ Applicable in the absence of exposure and benchmark limits	✔ Considers occupational, environmental & consumer exposure
		✔ Stoffenmanager® is included in the official REACH Guidance (R.14) document as a recommended tool. Meaning the European Commission officially recognizes Stoffenmanager as instrument to comply with the REACH regulation	✔ Not only qualitative risk asessemnt, but also semi-quantitative risk profiling,is feasible

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

future, since conducting risk assessment for each individual nanomaterial on a case-by-case basis would require a lot of resources as well as time, effort, and money.

CONCLUSIONS

This outlined Methodology on How to Create a Real-life relevant Risk Profile for a Given Nanomaterial relates to existing risk assessment practice under the current regulatory framework for the safe use of chemicals (i.e., REACH) and its future evolution towards an inclusion of provisions for nanoforms in ECHA guidance documents and a revision of REACH annexes to specifically address NMs.

The present paper gives guidance on how to create a risk profile for a given nanomaterial (e.g., determine which materials and/process operation pose greater risk, where these risks occur in the lifecycle, and the impact of these risks) using state-of-the-art safety assessment approaches/tools (ECETOC TRA, Stoffenmanager Nano and ISO/TS 12901-2:2014). It focuses on giving concrete, practical guidance to industry and regulatory authorities (such as European agencies, scientific committees, national competent authorities) on how to deal with environmental health and safety aspects (EHS) when dealing with NMs and nano-enabled products.

NMs manufacturers need to stay in phase with the latest evolutions of the legislative framework for NMs. Currently, the overarching European chemical regulation, REACH, is undergoing adaptation of its annexes to clarify nanomaterial requirements. At the same time we see European Member States continue setting up national nanomaterial registers. In this context, putting NMs in the European market has become increasingly difficult and costly, thus significantly hampering the innovation potential of the region.

Some of the nanosafety projects (NANoREG, NanoReg2, ProSafe) financed by the European Union intend to support regulation; these collect large quantities of comparable and consolidated data on toxicological endpoints. This is a first step towards a facilitated use of grouping and read-across for NMs, thus improving the quality of dossiers and reducing their cost. At international level the OECD is actively supporting grouping and read-across for NMs[57] and undertakes continued efforts to deliver a sustainable policy framework that ensures safe products and a positive environment for innovation.

The presented approach may be valuable both for policy makers/regulators and as well as industry. Policy makers/regulators can predominantly benefit from using the concept to prioritise those NMs and/or applications that need to be addressed most urgently. Industry can use the approach as a forward-looking strategy aiming at making safety assessment practical and economically efficient.

However, it needs to be emphasised that the field of nanomaterial risk assessment is evolving, and the methodology provided is based on the current available knowledge developed in diverse European research projects and other international organisations and committees. In the future, the methodology presented in this article may therefore be revised in the light of new scientific knowledge.

ACKNOWLEDGEMENTS
This work was supported by ongoing projects that received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no 646155 (INSPIRED), grant agreement no 646296 (Hi-Response) and grant agreement no 691095 (NANOGENTOOLS).

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jchas.2017.06.002.

REFERENCES

1. Beumer, K.; et al. Emerging technologies in India: developments, debates and silences about nanotechnology. *Sci. Public Policy*, **2013**, *40*(5), 628–643.
2. Sargent, J. F. Jr *Nanotechnology: A Policy Primer*. 2016.
3. Subramanian, V.; et al. Sustainable nanotechnology decision support system: bridging risk management, sustainable innovation and risk governance. *J. Nanopart. Res.* **2016**, *18*(4), 1–13.
4. Aruna, K.; et al. A systematic review on nanomaterials: properties, synthesis and applications. *i-Manager's J. Future Eng. Technol.* **2015**, *11*(2), 25.
5. Savolainen, K.; et al. *Nanosafety in Europe 2015–2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations*; Finnish Institute of Occupational Health: Helsinki, 2013.
6. Krug, H. F. Nanosafety research–are we on the right track? *Angew. Chem. Int. Ed.* **2014**, *53*(46), 12304–12319.
7. Bleeker, E. A. J.; et al. Considerations on the EU definition of a nanomaterial: science to support policy making. *Regul. Toxicol. Pharmacol.* **2013**, *65*(1), 119–125.
8. Hankin, S. M.; et al. *Governance of nanotechnology: context, principles and challenges*; Managing Risk in Nanotechnology. Springer, 2016, pp. 29–49.
9. Aithal, P. S.; et al. *Nanotechnology Innovations and Commercialization–Opportunities, Challenges & Reasons for Delay*. 2016.
10. Justo-Hanani, R.; et al. European risk governance of nanotechnology: explaining the emerging regulatory policy. *Res. Policy*, **2015**, *44*(8), 1527–1536.
11. Wijnhoven, S. W. P.; et al. Nano-silver–a review of available data and knowledge gaps in human and environmental risk assessment. *Nanotoxicology*, **2009**, *3*(2), 109–138.
12. Mattsson, M.-O.; et al. The changing face of nanomaterials: risk assessment challenges along the value chain. *Regul. Toxicol. Pharmacol.* **2016**, *84*, 105–115.
13. Hutchison, J. E. *The Road to Sustainable Nanotechnology: Challenges, Progress and Opportunities*; ACS Publications, 2016.
14. Schulte, P. A.; et al. Taking stock of the occupational safety and health challenges of nanotechnology: 2000–2015. *J. Nanopart. Res.* **2016**, *18*(6), 1–21.
15. Clark, K.; et al. Limitations and information needs for engineered nanomaterial-specific exposure estimation and scenarios: recommendations for improved reporting practices. *J. Nanopart. Res.* **2012**, *14*(9), 970.
16. NIOSH. *Evaluation of health hazard and recommendations for*

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

occupational exposure to titanium dioxide. NIOSH Current Intelligence Bulletin. 2005.
17. Aitken, R. A.; et al. *Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIP-oN 3)-Final Project Report*; European Commission, 2011.
18. Eastlake, A. C.; et al. Refinement of the nanoparticle emission assessment technique into the nanomaterial exposure assessment technique (NEAT 2.0). *J. Occup. Environ. Hyg.* **2016**, *13*(9), 708–717.
19. Van Duuren-Stuurman, B.; et al. Stoffenmanager nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. *Ann. Occup. Hyg.* **2012**, mer113.
20. ISO. *ISO/TS 12901-2:2014. Nanotechnologies–Occupational Risk Management Applied to Engineered Nanomaterials–Part 2: Use of the Control Banding Approach*. 2014.
21. ECETOC AISBL. *Targeted Risk Assessment User Guide for the Integrated Tool TRAM Version 3 Update to Version 3.1*; European Centre for Ecotoxicology and Toxicology of Chemicals, 2014 www.ecetoc.org.
22. SCENIHR. *Opinion on the Scientific Basis for the Definition of the Term "Nanomaterial"*; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), European Commission: Brussels, 2010.
23. Environment Agency Austria. *Methodology for Identification and Assessment of Substances for Inclusion in the List of Restricted Substances (Annex II) under the RoHS2 Directive*. 2014, http://www.umweltbundesamt.at/fileadmin/site/umweltthemen/abfall/ROHS/finalresults/Annex1_Manual.pdf.
24. Eisenberg, D. A.; et al. *Risk assessment, life cycle assessment, and decision methods for nanomaterials*. Nanomaterials in the Environment. 2015, pp. 383–419.
25. European Chemicals Agency (ECHA). *Guidance in a Nutshell – Chemical Safety*. 2009.
26. European Chemicals Agency. *Chemical Safety Report – An Illustrative Example*. 2012.
27. European Chemicals Agency. *Guidance on Information Requirements and Chemical Safety Assessment, vol. 12,* 2015. Chapter R.
28. REACHnano Consortium. *Guidance on Available Methods for Risk Assessment of Nanomaterials*. 2015 www.lifereachnano.com.
29. CEFIC (AISBL),; VCI e.V. *REACH Practical Guide on Exposure Assessment and Communication in the Supply Chains Part IV: Supplement Exposure Estimation*. 2010.
30. Gerritsen-Ebben, R.; Brouwer, D.; van Duuren-Stuurman, B.; Puijk, I.; et al. *NANEX – Development of Exposure Scenarios for Manufactured Nanomaterials; Occupational Exposure Scenarios*. 2010.
31. Beaudrie, C. E. H.; et al. Horses for courses: risk information and decision making in the regulation of nanomaterials. *J. Nanopart. Res.* **2011**, *13*(4), 1477–1488.
32. Pereira, A.; et al. *Control Banding applied to engineered nanomaterials: short review*; Occupational Safety and Hygiene V. CRC Press/Balkema, 2017, pp. 323–328.
33. Brouwer, D. H. Control banding approaches for nanomaterials. *Ann. Occup. Hyg.* **2012**, *56*(5), 506–514.
34. ISO. *ISO/TS 12901-2:2014. Nanotechnologies – Guidelines for occupational risk management applied to engineered nanomaterials – Part 2*. 2014.
35. Liguori, Biase. et al. Control banding tools for occupational exposure assessment of nanomaterials–ready for use in a regulatory context? *NanoImpact,* **2016**, *2*, 1–17.
36. Van Duuren-Stuurman. et al. Stoffenmanager nano version 1. 0: a web-based tool for risk prioritization of airborne manufactured nano objects. *Ann. Occup. Hyg.* **2012**, *56*(5), 525–541.
37. OECD. *Harmonized Tiered Approach to Measure and Assess the Potential Exposure to Airborne Emissions of Engineered Nano-Objects and their Agglomerates and Aggregates at Workplaces*. 2015.
38. OECD. *Guidance Manual owards the Integration of Risk Assessment into Life Cycle Assessment of Nano-Enabled Applications*. 2015.
39. European Chemicals Agency. *Guidance on Information Requirements and Chemical Safety Assessment, Part A: Introduction to the Guidance Document*. 2010.
40. European Commission. *Guidance on the Protection of the Health and Safety of Workers from the Potential Risks Related to Nanomaterials – Guidance for Employers and Health and Safety Practitioners*. 2013.
41. Hristozov, D.; et al. Frameworks and tools for risk assessment of manufactured nanomaterials. *Environ. Int.* **2016**, *95*, 36–53.
42. Stone, V.; et al. ITS-NANO-prioritising nanosafety research to develop a stakeholder driven intelligent testing strategy. *Part. Fibre Toxicol.* **2014**, *11* (1), 1.
43. Som, C.; et al. *LICARA Guidelines for the Sustainable Competitiveness of Nanoproducts*. 2014. Dübendorf, St. Gallen.
44. Bos, P. M. J.; et al. The MARINA risk assessment strategy: a flexible strategy for efficient information collection and risk assessment of nanomaterials. *Int. J. Environ. Res. Public Health,* **2015**, *12* (12), 15007–15021.
45. Sikorová, L.; et al. *Building Exposure Scenarios for Safety Management of Engineered Nanomaterials*. 2016.
46. Malsch, I.; et al. Supporting decision-making for sustainable nanotechnology. *Environ. Syst. Decis.* **2015**, *35*(1), 54–75.
47. Bremmer, H. J.; et al. *Cosmetics Fact Sheet. To Assess the Risks for the Consumer. Updated Version for ConsExpo 4*. 2006.
48. van Harmelen, T.; et al. LICARA nanoSCAN-A tool for the self-assessment of benefits and risks of nanoproducts. *Environ. Int.* **2016**, *91*, 150–160.
49. Hansen, S. F.; et al. NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products. *J. Nanopart. Res.* **2014**, *16*(1), 1–25.
50. Jensen, K. A.; et al. NanoSafer vs. 1.1-nanomaterial risk assessment using first order modeling. *6th International Symposium on Nanotechnology, Occupational and Environmental Health.* Japan, 2013.
51. Meesters, J. A. J.; et al. Multimedia modeling of engineered nanoparticles with SimpleBox4nano: model definition and evaluation. *Environ. Sci. Technol.* **2014**, *48*(10), 5726–5736.
52. Höck, J.; et al. *Guidelines on the Precautionary Matrix for Synthetic Nanomaterials*; Federal Office for

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002

Public Health and Federal Office for the Environment: Bern, 2010.
53. Vance, M. E.; et al. Nanotechnology in the real world: redeveloping the nanomaterial consumer products inventory. *Beilstein J. Nanotechnol.* **2015**, *6*(1), 1769–1780.
54. Eastlake, A.; et al. Can control banding be useful for the safe handling of nanomaterials? A systematic review. *J. Nanopart. Res.* **2016**, *18*(6), 1–24.
55. Targeted Risk Assessment Ecetoc, Technical Report no. 93. European Centre for Ecotoxicology and Toxicology of Chemicals, 2004.
56. NANoREG Consortium. *D1.11 on NANoREG Final Framework*. 2017. in preparation.
57. OECD. *Grouping and Read-Across for the Hazard Assessment of Manufactured Nanomaterials*. 2016.

Please cite this article in press as: Schimpel, C. et al1., A methodology on how to create a real-life relevant risk profile for a given nanomaterial. J. Chem. Health Safety (2017), http://dx.doi.org/10.1016/j.jchas.2017.06.002