The applicability of chemical alternatives assessment for engineered nanomaterials

Hjorth, Rune; Hansen, Steffen Foss; Jacobs, Molly; Tickner, Joel; Ellenbecker, Michael; Baun, Anders

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Authors **(in order)**	Rune Hjorth[*†]
	Steffen Foss Hansen[†]
	Molly Jacobs[‡]
	Joel Tickner[‡]
	Michael Ellenbecker[‡,§]
	Anders Baun[†]
Affiliation	†Department of Environmental Engineering, Building 115, Technical University of Denmark, Kongens Lyngby, 2800, Denmark [‡]University of Massachusetts Lowell, Lowell Center for Sustainable Production, Lowell, MA 01854, USA [§]University of Massachusetts Lowell, Massachusetts Toxics Use Reduction Institute, Lowell, MA 01854, USA
E-mails	Rune Hjorth (ruhj@env.dtu.dk) Steffen Foss Hansen (sfha@env.dtu.dk) Molly Jacobs (mjacobs@envhealth.net) Joel Tickner (joel_tickner@uml.edu) Michael Ellenbecker (michael@turi.org) Anders Baun (abau@env.dtu.dk)

[*]To whom correspondence may be addressed

ABSTRACT

The use of alternatives assessment to substitute hazardous chemicals with inherently safer options is gaining momentum worldwide as a legislative and corporate strategy to minimize consumer, occupational, and environmental risks. Engineered nanomaterials represent an interesting case for alternatives assessment approaches as they can be considered both emerging "chemicals" of concern, as well as potentially safer alternatives to hazardous chemicals. However, comparing the hazards of nanomaterials to traditional chemicals or to other nanomaterials is challenging and critical elements in chemical hazard and exposure assessment may have to be fundamentally altered to sufficiently address nanomaterials. The aim of this paper is to assess the overall applicability of alternatives assessment methods for nanomaterials and outline recommendations to enhance their use in this context. This paper focuses on the adaptability of existing hazard and exposure assessment approaches to engineered nanomaterials as well as strategies to design inherently safer nanomaterials. We argue that alternatives assessment for nanomaterials is complicated by the sheer number of nanomaterials possible. As a result, the inclusion of new data tools that can efficiently and effectively evaluate nanomaterials as substitutes are needed to strengthen the alternatives assessment process. However, we conclude that with additional tools to enhance traditional hazard and exposure assessment modules of alternatives assessment, such as the use of mechanistic toxicity screens and control banding tools, alternatives assessment can be adapted to evaluate engineered nanomaterials both as potential substitutes for chemicals of concern and to ensure safer nanomaterials are incorporated in the design of new products.

Keywords: Alternatives assessment, Engineered nanomaterials, Hazard, Safety by design, Decision-making

INTRODUCTION

There are increasing scientific, market and policy concerns about the human health and environmental impacts of toxic chemicals in industrial manufacturing processes and in everyday consumer products. In response, government and private sector chemicals management policies have sought to minimize the risk of harm primarily by controlling exposure to chemical toxicants. Over the last decade there has been growing pressure to reduce or eliminate risks associated with chemicals of high concern by requiring substitution with safer alternatives. Examples of this are the European Union's chemical legislation REACH and state level regulation in the U.S. implemented in Washington, Maine and California, which require assessments of hazardous chemicals classified as "priority" or "very high concern" to identify safer and feasible chemical or process substitutes (Cowan et al. 2014). Central to these regulatory programs and similar activities by leading corporations, including product manufacturers and retailers, is the use of alternatives assessment (Lavoie et al. 2010; NRC 2014).

Alternatives assessment is a methodology for identifying, comparing and selecting safer alternatives to chemicals of concern, including those in materials, processes or technologies. A primary goal of an alternatives assessment is to reduce potential harm to humans and the environment by selecting a safer chemical to achieve a specific function for a given application (i.e., solvency, electrical conduction, tensile strength, etc.). Engineered nanomaterials can be considered both as emerging "chemicals" of concern, as well as potential substitutes for highly toxic "bulk" chemicals in specific applications. However, evaluating the hazards and potential exposures to these novel materials has proven challenging; nano-specific hazard and risk research have lagged and technical guidance on how to complete such assessments is only slowly being developed. Nonetheless, product

design and redesign decisions that may incorporate engineered nanomaterials are being made now. As such, regulators, companies, and other stakeholders need comprehensive yet efficient ways to evaluate hazards and potential exposures to nanomaterials in substitution decisions. As alternatives assessment compares potential chemical and design alternatives to a chemical of concern, the goal is not a detailed evaluation of safety but rather to characterize safer options and identify possible unintended risk trade-offs from a substitution decision. Alternatives assessment frameworks are designed to be generic and flexible (NRC 2014) and therefore should in theory be applicable to nanomaterials. Yet given the unique physical and chemical characteristics of nanomaterials, an evaluation of specific modules within existing alternatives assessment frameworks, especially those focused on hazard and exposure evaluation, is needed to ensure potential adverse effects associated with nanomaterials are appropriately considered.

The aim of this paper is to assess the overall applicability of alternatives assessment for nanomaterials and outline recommendations to enhance the use of this methodology to ensure the safer consideration of nanomaterials in manufacturing processes and products. This paper first briefly reviews the scope of alternatives assessment frameworks and focuses on how such frameworks evaluate hazard, exposure and physical chemical characteristics – critical elements of an alternatives assessment that may differ between traditional bulk and engineered nanomaterials. We then address central questions relevant to the applicability of alternatives assessment in the evaluation of nanomaterials and analyze the feasibility of the hazard and exposure modules for nanomaterials as well as the use of alternative tools to address and reduce risk. Finally, we provide recommendations and suggest modifications to the existing alternatives assessment frameworks to better aid the selection of safer nanomaterials.

SCOPE OF ALTERNATIVES ASSESSMENT: THE IC2 AND NRC FRAMEWORKS

Alternatives assessment involves: (a) identifying the chemical of concern; (b) identifying candidate alternatives that can achieve the same purpose or function served by the chemical of concern for a given application; (c) evaluating and comparing alternatives and the chemical of concern based on a range of human and environmental health endpoints at critical lifecycle points (e.g., manufacturing, use, disposal), as well as evaluating and comparing technical and economic feasibility characteristics; and (d) selecting the preferred feasible alternative that meets financial and technical requirements and minimizes health and environmental impacts (OECD, 2013; NRC, 2014; Jacobs et al. 2015).

While over a dozen alternatives assessment frameworks have been published over the last decade by academic institutions, non-governmental and governmental organizations, we focus on two recently published frameworks: the Interstate Chemical Clearinghouse (IC2) "Alternatives Assessment Guide" and the National Research Council (NRC) "Framework to Guide Selection of Safer Chemicals" (IC2 2013; NRC 2014). These were chosen as they reflect the most current and the most comprehensive methodological frameworks for alternatives assessment. Figures 1 and 2 outline the scope of the IC2 and NRC frameworks, respectively.

Both frameworks evaluate an array of similar endpoints to assess environmental and human health hazards, including carcinogenicity, reproductive and developmental toxicity, endocrine disruption, dermal and respiratory sensitization, mutagenicity, aquatic toxicity, among others. In total, the NRC framework outlines 14 human health hazard endpoints while the IC2 framework identifies a range of 6-18 endpoints. This range reflects

three levels of depth in the IC2 framework, from a quick scan using tools such Washington State's "Quick Chemical Assessment Tool" to an "expanded" hazard assessment. Both frameworks depend on publicly available data to categorize hazards, including the United Nations Globally Harmonized System for the Classification and Labeling of Chemicals (GHS) and authoritative lists such as classification of carcinogens by the International Agency for Research on Cancer (IARC). The chemical of concern and the prospective alternatives are compared in each framework against a series of mammalian and ecotoxicity metrics for each of the endpoints addressed. To facilitate comparisons, both frameworks assign hazard classification levels using ranking 3-, 4-, or 5-point scales, (e.g., very high, high, moderate, low, very low). While both frameworks incorporate a range of traditional toxicological and in-silico approaches to evaluating hazard, the NRC framework specifically calls for greater use of high throughput data both in filling data gaps and eventually serving as primary hazard data.

Exposure is addressed somewhat differently in the NRC and IC2 frameworks. The IC2 framework addresses exposure considerations only after the assessment of hazard, performance and cost in order to examine potential trade-offs with identified alternatives. The NRC framework considers factors that impact the "inherent exposure" of a chemical simultaneously along with ecological and human health hazards, i.e., the potential for reduced exposure due to inherent properties of the alternatives chemicals (as opposed to industrial hygiene techniques such as engineering controls or personal protective equipment). The NRC framework also considers routes of exposure and associated levels when integrating the evidence related to human and ecological toxicity among alternatives. In both frameworks, the result of the characterization of exposure is to identify relative differences in the exposure potential among alternatives, i.e., substantially equivalent, inherently preferable, or

potentially worse (higher levels of exposure). Thus the primary purpose of exposure evaluation is not to assist a quantification of the risks but rather to rank the alternatives and their exposure profiles from most to least desirable. Quantitative exposure assessment, as required in risk assessment, is included in the IC2 framework as "advanced" level where it is required, such as those assessments that are regulatory-based and dependent on risk characterization.

It is important to note that the field of life cycle assessment is also demonstrating the applicability of its methods and tools for the evaluation of nanomaterial product alternatives as reviewed in a recent case study by Tsang and colleagues (2014). While the IC2 framework and the NRC framework both include components that address life cycle impacts, both defer to existing LCA methodologies when the evaluation of alternatives need to consider life cycle impacts beyond a robust evaluation human and environmental hazards and evaluation of intrinsic exposure concerns, including impacts such as global warming potential, acidification and eutrophication (IC2 2013; NRC 2014).

IS NOVELTY OF NANOMATERIALS A BARRIER TO THEIR EVALUATION?

As described above, the NRC and IC2 alternatives assessment frameworks require data on an array of attributes of potential alternatives in order to make decisions about which is safer. However, a key question affecting the applicability of alternatives assessment frameworks for their use in evaluating nanomaterials is the novelty of these materials.

The UK Royal Commission on Environmental Pollution (RCEP) (2008) defines material novelty by distinguishing between four types of novel materials: (1) new materials hitherto unused or rarely used on an industrial scale, e.g., carbon nanotubes (CNTs); (2) new forms of existing materials with characteristics that differ significantly from familiar or

naturally occurring forms, e.g., engineered gold nanoparticles; (3) new applications for existing materials or existing technological products formulated in a new way, e.g., cerium oxide nanoparticles used as a fuel additive; and (4) new pathways and destinations for familiar materials that may enter the environment in forms different from their manufacture and envisaged use (RCEP 2008).

For new materials hitherto unused or rarely used on an industrial scale (RCEP category 1), alternatives assessment is an important tool to facilitate safer design. An example of hitherto unused nanomaterials is CNTs, first discovered in 1991. CNTs are high aspect ratio cylindrical nanostructures that can vary with regards to the number of carbon atoms layers and diameter (up to 20 nm), length (from a few micrometers up to millimeters) and surface functionalization. Due to variations in physico-chemical properties, the biological activity of CNTs vary as well (Donaldson et al. 2011). Some potential uses of CNTs are truly novel and exploit properties that are nano-related, such as their use in advanced memory devices. In these advanced products, nanomaterials may be far superior to conventional chemicals and materials from a performance perspective. Alternatives assessment in this context could be applied during the design-phase of research and development efforts to compare individual CNTs (different size, functionalization, shape, etc.,) or to select the safest CNT that also achieves the necessary function and performance. While alternatives assessments have routinely been employed reactively – identifying alternatives to chemical of concern – the approach is also useful to proactively design-out inherent hazards during the materials and product development stage.

Nanoscale zero-valent iron (nZVI) is an example of a "new form of existing materials with characteristics that differ significantly from familiar or naturally occurring forms" (RCEP category 2). This is due to the significantly increased surface area that nZVI

obtains at the nanoscale, which leads to higher reactivity per mass unit compared to larger iron particles. TiO_2 nanoparticles are an example of a nanomaterial that falls into the third RCEP category of novel categories as new applications of nanoscale TiO_2 keep emerging, even though the use of TiO_2 in itself is not new. RCEP category 4 include biodegradable polymeric particles such as poly(lactide-co-glycolides) (PLGA) as such polymer nanoparticles can be engineered to transgress biological membranes e.g., for use in drug delivery (Hansen et al. 2013).

For all four types of novel materials, a fundamental question confronting the use of alternatives assessment for their evaluation is data availability. For any newly engineered chemical or material, there is a natural time course in generating data needed for conducting an alternatives assessment, most notably data on hazards and exposure. Lack of hazard data is a persistent challenge confronting hazard assessments, as complete hazard information on the broad range of potential health outcomes - even for chemicals that have been used for over a century - remains an issue. The characterization of exposure is also hindered by data gaps and detailed information about exposure significantly lags data on hazard – an issue plaguing nanomaterial risk characterization.

However, given the relatively rapid timeframes by which decisions are being made on chemical substitution as well as design of new products that are incorporating nanomaterials, one defining feature of the alternatives assessment methodology is to make use of the entirety of the data, wherever it exists, for informed decision-making. While engineered nanomaterials are clearly novel, we have learned a lot about their properties and their novel characteristics. Despite lacking human and ecotoxicity endpoints for many nanomaterials, nanotoxicology has been an area of intensive research for over a decade. Given that data – albeit incomplete – are available for many nanomaterials, alternatives assessment methods

include techniques for making data gaps explicit and considered in the overall assessment, the novelty of nanomaterials in-and-of-itself is not sufficient to render alternatives assessment inapplicable for these materials. Quite the opposite: alternatives assessment of nanomaterials can help drive decisions down safer paths using whatever data is available for novel materials.

CHALLENGES TO EVALUATING ENGINEERED NANOMATERIALS

Current hazard assessment methods

Central to the evaluation of alternatives in both the IC2 and NRC frameworks is the assessment of hazard. Yet are these hazard assessment approaches appropriate for the evaluation of nanomaterials? The identity of a nanomaterial and variation within the same chemical form of a nanomaterial poses a challenge for alternatives assessment. Nanomaterials not only differ substantially compared to the bulk form of a given substance, but also within the same nanomaterial e.g., CNTs, TiO_2 and Ag exist in numerous sizes, shapes, and configurations as nanoparticles. For example, multi-walled CNTs (MWCNTs) are emerging as potential alternatives for halogenated flame retardants. For a given alternatives assessment to identify safer alternatives to halogenated flame retardants, the question becomes, which MWCNT or which mixture of MWCNTs should be assessed, as there are tens of thousands of possible variations of MWCNTs. Alternatives assessment frameworks were originally developed to evaluate chemicals, not materials. In the case of chemicals, each is unique and can be identified through its unique Chemical Abstract Service (CAS) number. There is no analogous system to uniquely identify nanomaterials, or any material for that matter, as each differs based on specific physical and chemical characteristics, such as size, coating, surface charge, and surface chemistry. Due to lack of available data and lack of characterization of

the particular nanoparticle studied in the available studies, hazard assessment of a specific particle becomes difficult, which was identified as a specific challenge in a recent comparative hazard assessment of nanosilver and bulk silver (Heine and Sass 2013). Alternatively, a hazard assessment based on data for particles of the same material (e.g., a hazard assessment for silver nanoparticles in general) will only give an overall description of, for instance, silver nanoparticles, without emphasis on the specific particle at hand, which fails to distinguish the differences in toxicity between similar particles with different properties. The issue becomes even further challenged by the fact that nanomaterials incorporated into commercial products are not always of the same level of purification as those required in research studies.

Dose-metrics used to characterize hazards poses another challenge in the hazard assessment module for nanoparticles. For conventional chemicals, mass-based metrics (e.g., mg/kg) are used for assigning of concern-level cut-off values for many endpoints in existing hazards assessment tools. For many types of nanomaterials, dose-metrics based on specific surface area or particle number and/or size distribution/agglomeration state have been shown more relevant for pulmonary toxicity assessment (Oberdorster et al. 2007) as well as for ecotoxicity of SiO_2 nanoparticles (Van Hoecke et al. 2009). However, for Ag, Cu, and Zn nanoparticles, ion release is a key factor for toxicity, whereas for other particles, like TiO_2, the crystal structure may play a major role (Hartmann 2011). While this may seem to be a barrier to generalized rules of thumb to characterize hazards based on the properties of the nanoparticles, an understanding of which properties are related to hazard is beginning to emerge for different classes of nanomaterials.

Current exposure characterization and assessment methods

As with hazard assessment, exposure assessment of nanomaterials is challenging as the behavior of these materials in the environment is dependent not only on the specific physicochemical properties of the material, but also on the environment into which the nanomaterials are released (Ganzleben and Hansen 2012; Hartmann et al. 2014). As noted by Ganzleben and Hansen (2012) it is often more important to understand the specific properties of nanomaterials released from diffuse and point sources after the nanomaterials has undergone initial transformation reactions, than it is to understand the specific properties of the pristine versions - but only rarely is such information available (Stone et al. 2010; Hartmann et al. 2014). Given the particular properties of nanomaterials, researchers have suggested that existing environmental fate and transport models used for chemicals are probably generally not applicable for these materials (Ganzleben and Hansen 2012). As in the case of hazard identification, nanomaterials differ from most conventional dissolved chemicals, in the sense that the spatial distribution of mass concentration is likely not to be the most relevant parameter with which to describe the state of the environment (Quik et al. 2011; Ganzleben and Hansen 2012). Recently, a few models have been proposed for application to environmental exposure assessment of nanomaterials e.g., probabilistic mass flow analysis and kinetic modeling that do attempt to take agglomeration and sedimentation into account; validation of the models is difficult, however (Gottschalk et al. 2013; Meesters et al. 2014).

When it comes to occupational exposure, highly specialized research and measurement techniques are required in order to quantify the specific nanomaterial exposure due to mixture with other particle sources in the factory and the surrounding environment, as well as aerosol dynamics including agglomeration and deposition (Sipenbush, 2014; Liguori

et al. 2012). Thus far, researchers have focused on the development of number-based exposure metrics, using instrumentation that ranges from complex, difficult to use and expensive (e.g., scanning mobility particle sizers that measure particle number concentration as a function of particle size) to relatively simple and inexpensive (e.g., hand-held condensation particle counters that measure the total number of nanometer-sized particles). The use of the first category is likely to be limited to research, while the second category is a likely candidate for use in measuring against number-based occupational exposure limits.

Using existing chemical modeling approaches of worker exposure is hampered by the fact that they very often rely on an occupational exposure limit or similar values having been established, which only exists for a few specific nanomaterials. Most exposure modeling tools furthermore use existing physico-chemical properties and do not consider nanospecific properties that have been noted as being important e.g., particle shape, surface area, surface energy, surface chemistry, state of dispersion and state of agglomeration (Aitken et al. 2011).

OPPORTUNITIES AND RECOMMENDATIONS FOR THE USE OF ALTERNATIVES ASSESSMENTS OF ENGINEERED NANOMATERIALS

A focus on functional use

A fundamental question related to the scope of alternatives assessment is "why is the material/chemical present in the product?" What properties are needed, that an alternative material/chemical should also have in order to achieve the desired function and performance? The approach of focusing on function and broadly exploring alternatives to

meet that function, including considering the necessity of that function or performance has been termed "functional substitution" (Tickner et al. 2015). Perhaps surprisingly, this question of "why is the material present" can sometimes be difficult to answer for products containing nanomaterials, as some products merely utilize the nanomaterial for commercial purposes (e.g., a branding of a product). If such a nanomaterial serves no necessary function or is completely redundant and is potentially risky for human or environmental health, it may be easiest to simply avoid using that material.

Identifying and designing safer nanomaterials

As nanomaterials can be purposefully manipulated down to a single atom, one has the opportunity to modify a material to suit the needs of the market. Similarly, using emerging scientific knowledge about the properties, toxicity and exposure to nanomaterials, it may be possible to design safer nanomaterials. Therefore, a nanomaterial similar to the original but with specific modifications that reduce intrinsic hazard and exposure potential could very well prove to emerge from an alternatives assessment as the best alternative to the original. Morose (2010) described five principles of "Design for Safer Nanotechnology" that can direct efforts into reducing nanomaterial risk by modifying the nanomaterial or its use by the following principles as seen in Figure 3.

Principle #5 "Reduce the quantity" will obviously reduce potential risks just as changing to a less toxic material (principle #2). Principle #5 is especially true for nanomaterials that are necessary to achieve an essential function. Thus, reducing risk to people and the environment depends on mitigating exposure potential. Principles #1, #3 and #4 all rely on modifying the nanomaterial to engineer a material that is inherently safer.

Designing safer nanomaterials incorporates occupational, consumer, and environmental considerations. Traditional risk reduction strategies, such as exposure controls for consumers may not necessarily also decrease the risk in an occupational setting or decrease the environmental impact of the material, as the exposure scenarios can be quite different. However, reducing the hazard of the material will benefit safety in any situation.

Intrinsic hazard evaluation in alternatives assessment: learning from safer nanomaterial design

The current state of nanosafety science is still not mature enough to accurately describe what parameters control toxicity of nanomaterials. This lack of mechanistic understanding is a major roadblock for the use qualitative or quantitative tools to estimate toxicity, such as structure activity relationships, modeling or read-across approaches. Nonetheless, general trends are emerging which could guide the selection of safer nanomaterials. For instance, in 2013 Burello and Worth published a rule for designing safer nanomaterials (Burello and Worth 2013). The rule is based upon earlier work on prediction of oxide nanoparticle toxicity (Burello and Worth 2011; Zhang et al. 2012) and relies on the calculation of energy band structures to assess the particle's potential to induce oxidative stress by interfering with the cellular redox equilibrium. Since oxidative stress is a general mechanism of toxicity for a range of nanoparticles, they propose that generation of safer nanoparticles can be helped along through simple band energy calculations.

To mitigate oxidative stress Burello and Worth suggest several strategies, including modifying the size of the particle to change the energy band structure or masking the reactivity with the use of coatings, such as SiO_2 or surface functionalization (Burello and

Worth 2013). These are consistent with principle #1 and #3 of Morose's (2010) SAFER principles (Figure 3). Gass et al. (2013) showed experimentally that SiO_2 encapsulated nanoparticles (CeO_2, ZnO, Fe_2O_3 and Ag) prove less toxic than their uncoated versions. Although some properties of the core material are left intact within the SiO_2-shell (magnetic, plasmonic, phosphorescent or optical), other properties were also affected. For instance, the catalytic abilities of CeO_2 disappeared after encapsulation as they rely on surface interactions. As for CeO_2, the SiO_2 encapsulation also removed the photocatalytic properties of ZnO, which is unwanted in cosmetics.

Other studies on metal and metal oxide nanoparticles have revealed additional strategies to minimize toxicity. Ivask et al. (2013) conducted a review of the toxic action of Ag, ZnO and CuO nanoparticles and concluded that three factors are driving their toxicity: dissolution, cellular uptake and induction of oxidative stress. As the authors state, this knowledge can both aid the creation of particles that are "toxic by design" (e.g., Ag nanoparticle in medical dressings) as well as particles that are safer by design. For example, the rate of dissolution for ZnO nanoparticle can be controlled through Fe doping, which in turn does reduce ZnO toxicity (George et al. 2010). However, it should be noted that a reduced rate of dissolution could perhaps also be interpreted as an increased persistence of the nanoparticle and give rise to further dissemination in the environment. Similar doping approaches have also proven effective to reduce oxidative stress of TiO_2 nanoparticles. For instance, Wake et al. (2004) showed how doping TiO_2 nanoparticles with 1% (w/w) manganese reduced free radical generation by over 90 %, increased UVA absorption and introduced free radical scavenging behavior.

To address cellular uptake of nanoparticles, size is clearly a paramount parameter (Oberdorster et al. 2007), and as Burello and Worth (Burello and Worth 2013)

stated, also a way to address oxidative stress. Surface charge is unquestionably another key factor in understanding and controlling both nanoparticle uptake as well as toxicity (Harper et al. 2011; Fröhlich 2012). It is, however, important to emphasize that nanotoxicology and nanoparticle behavior remains complex and influenced by a multitude of other physico-chemical properties, such as hydrophilicity, aggregation/agglomeration and shape. Ultimately, each of these parameters can potentially be optimized for both toxicity reduction and functionality.

Carbon nanomaterials are structurally quite diverse as well as unique among nanomaterials and certain design considerations are emerging to address safety. Yan et al. (2011) identified five ways to reduce the toxicity of carbon nanomaterials: (1) creating a more hydrophilic surface; (2) lowering the adsorbability; (3) changing the size; (4) using the less toxic double-walled carbon nanotubes instead of single-walled carbon nanotubes; and (5) modifying the surface charge to avoid aggregation/agglomeration. All of these green engineering strategies have been observed to lower the toxicity of carbon nanomaterials.

For high aspect ratio nanomaterials (HARNs) like CNTs additional considerations have to be taken into account due to their resemblance to asbestos fibers. Donaldson et al. (2011) describes the so-called fiber pathogenicity paradigm "that dictate whether or not a fiber will be pathogenic when inhaled" depending on its width, length and biopersistence and concludes that their studies "point towards the likelihood that all HARNs will conform to the general fiber pathogenicity paradigm, although further research is needed" (Donaldson et al. 2011). The paradigm dictates that a production of safer HARNs means creating HARNs that are short, thick and/or biodegradable. The suggested cutoff size values for 'safe' HARNs are > 3µm in width and <5 µm in length (Donaldson et al. 2011).

In addition to modifying existing nanomaterials, alternatives should also be sought among next generation nanomaterials that could outperform older generations, on both performance and safety. An example of this is cadmium-containing quantum dots, which likely will be replaced with less toxic materials such as luminescent carbon nanodots, graphene quantum dots, nanosized graphene or silicon quantum dots (Winnik and Maysinger 2013). Another possibility is to use alternatives assessment as a tool to evaluate whole technologies, as it is not necessarily limited in scope to only address a chemical/material of concern in a commercial product (e.g., CNTs in tennis rackets) - environmental remediation with nZVI could also be the focus of an alternatives assessment. Here alternative treatment options can be compared, rather than finding an alternative to a single component in a remediation technology.

The hunt for safer nanomaterials only seems to be intensifying as our understanding of nanotoxicology increases. In Europe multiple large international projects are currently working towards integrating safety consideration early into product design including Sanowork, GUIDEnano, NanoMile, and NanoReg. These projects generally have a strong focus on high-throughput testing and generating read-across principles for the safety assessment of nanomaterials. Though it is still too early to give specific advice on how this will feed into alternatives assessment, these research efforts will serve as critical sources of information on the future selection of safer nanomaterials.

Alternatives assessment has the opportunity to advance the identification and ranking of safer nanomaterials through its comparative approach and by systematically evaluating what is known/unknown about human and ecologoical toxicological endpoints. There is a need to incorporate knowledge emerging from research on green and safer nanotechnology into alternative assessment frameworks as research is progressing rapidly to

understand the physico-chemical characteristics predictive of harm, which will ultimately guide engineering design principles for nanomaterials. This recommendation is consistent with the NRC's own recommendations to enhance the use and evaluation of physicochemical properties in alternatives assessment in order "…to inform data gaps and guide the chemical design process." This is also consistent with Hansen et al. (2013) use of physicochemical properties of nanomaterials as "early warning signs" of harm.

While highly needed, the inclusion of a new suite of physiochemical properties relevant to factors that influence hazard characterization and environmental fate of nanomaterials such as those described above, e.g., size/shape, reactivity, and surface charge, is a complex task. A recent hazard assessment, which included nanosilver in the evaluation found that the research literature often failed to fully characterize the physicochemical characteristics of the study materials making such results unusable for subsequent hazard assessments (Heine and Sass 2013). Given the high diversity of nanomaterials, it cannot be expected that generic rules for "high," "medium" or "low" hazard rankings based on specific physiochemical properties would hold true for all types of nanomaterials. Thus future research should take a case-study approach and evaluate a range of commonly used nanomaterials (e.g., Ag, TiO_2, and CNTs) when undergoing method development.

Intrinsic exposure evaluation of nanomaterials in alternatives assessment: learning from safer nanomaterials design

The field of alternatives assessment has elevated the importance of selecting options that are less hazardous to human health or the environment based on the premise that minimizing hazard rather than exposure is the most effective strategy for preventing disease

and environmental damage (Jacobs et al. 2015). Yet it is rare for hazards to be completely eliminated and exposure mitigation should be considered, especially those factors that can reduce the intrinsic exposure potential of a given nanomaterial as exposure in many situations can be the easiest parameter to address. Also, consideration of intrinsic exposure is critical to understanding potential risk trade-offs that might occur between substitution options. Rather than complex exposure modeling, which is often required in risk assessment, simplified exposure estimates can likely meet the needs of most alternatives assessments where the core question to be answered is, "which chemical/material is safer".

Morose's (2010) safer nanomaterial design principles incorporate several attributes that are relevant to the evaluation of intrinsic exposure in alternatives assessment. These include principle #4 "encapsulation" and principle #5 "reduce the quantity". These concepts are already addressed in existing alternatives assessment frameworks. Both the NRC and IC2 frameworks include "quantity used" as a key metric in the evaluation of exposure. Similarly, both frameworks also include a number of physicochemical and/or processing and handling characteristics that influence the intrinsic exposure of a given chemical or nanomaterial, such as "binding strength/migration potential," "processing characteristics" and "particle size". Unlike the issue of intrinsic hazard evaluation where new evaluation tools are needed that link specific physicochemical characteristics of nanomaterials to varying hazard levels, existing approaches to consider intrinsic exposure in the NRC and IC2 frameworks may be sufficiently applicable for nanomaterials.

However, alternatives assessment methods for the evaluation of intrinsic exposure of nanomaterials could benefit from recent developments. A range of control banding tools has been developed as alternative approaches for risk management and these could be integrated into alternatives assessment where more detailed exposure

characterization is needed, such as in the context of regulatory requirements under REACH or California's Safer Consumer Products regulation. When there is a lack of quantitative exposure estimations, control banding provides a generic pragmatic approach to risk management by proposing a range of control measures (such as general ventilation, containment, etc.) according to the estimated range of "bands" of hazard and the range of "bands" of exposure" (ISO 2014). A number of control banding-type tools have already been developed for nanomaterials and they vary extensively in regard to scope and of domain of application, their types of algorithms, the extent to which, they rely on nanospecific information and finally, in their ranges and relative dynamics in protection (Liguori et al. 2012). The most simple exposure assessment tools categorize exposure potential into "High", "Medium" and "Low" based on the location of the nanoparticles in the process or products. For instance, in the framework known as NanoRiskCat developed by Hansen et al. (2014), the exposure potential is assumed to be high if the nanoparticles are airborne or suspended in liquids and considered to be medium and low, if the nanoparticles are surface bound and suspended in solids, respectively. Such a simple categorization employs knowledge about use characteristics as well as physicochemical characteristics and can be used to direct focus towards "designing exposure out" of the process and/or product (see Figure 4), which is consistent with Morose's (2010) SAFER principle #4 "encapsulation".

For the most sophisticated control banding tools such as NanoSafer (Jensen et al. 2013) and Stoffenmanager Nano (Duuren-Stuurman et al. 2012) the allocation of exposure bands takes a wide range of parameters into account such as the respirable rotating drum dustiness index; the activity handling energy factor; the total mass of material handled in each work cycle; the duration of work cycle; the pause between work cycles; the number of work cycles per day; the amount of nanomaterial handled in each transfer (spoon, bag, big-bag

etc.); the time required for each transfer (spoon, bag, big-bag etc.); the volume of the work room; and the air-exchange rate (Liguori et al. 2012).

In the IC2 alternatives assessment framework evaluated here as well as in many other available frameworks, the hazard module is followed by the exposure module. This ordering reflects an explicit decision-rule that exposures are likely to remain similar among alternatives for a particular function and application and that only those alternatives that demonstrate improved environmental and health attributes (i.e., hazard profiles) are evaluated, where necessary, with regard to exposure and other considerations such as cost. Interestingly, experts have recognized that hazard assessment will remain a significant challenge for many years to come when it comes to nanomaterials. For instance SCENIHR (2007) suggested that more emphasis should be placed on exposure characterization early in the assessment process. SCENIHR (2007) proposed a four-stage process which first focuses on identifying whether the manufacture, use and/or end of use disposal or recycling could result in exposure of humans or environmental species and ecosystems. This is followed by a characterization of the nature, level and duration of any exposure and then subsequently by an identification of the hazardous properties of any forms of the nanomaterial to which significant exposure is likely. While this approach was envisioned for use within the conventions of risk assessment, it could be adapted for alternatives assessment whereby a qualitative characterization of exposure potential is employed to interpret the hazard assessment findings. This is consistent with the NRC framework where inherent exposure potential (regardless of controls) is compared between options. An option with significantly lower exposure potential may, in some cases, be considered a safer alternative, even if a comprehensive hazard data set is not available.

Making decisions about nano-enabled alternatives

As stated earlier, alternatives assessment is not simply a comparative evaluation of hazard and exposure characteristics of the alternatives. Technical and economic feasibility as well as additional life cycle impacts are also examined and compared. However, alternatives assessment is not just a technical evaluation of these multiple attributes, it is directly tied to making a decision about a safer chemical, material or technology in either a design or substitution context.

Malloy and colleagues (2013) have comprehensively reviewed how various decision approaches (e.g., decision rules and logic) and decision tools (e.g., multi-criteria decision analysis or MCDA) are used in alternatives assessment to assist with decision-making. When a range of attributes with very heterogeneous data and information is being assessed, more formal decision analysis tools such as MCDA can be useful. Recent case studies, including assessments of alternatives that have considered nanomaterials have demonstrated the utility of using MCDA to aid decision-making (Malloy et al 2013; Tsang et al 2014; Linkov et al. 2007). MCDA involves applying decision criteria and weights to attributes that reflect stakeholder and decision-maker values that are inherent in the decision process. MCDA allows for the visualization and quantification of the tradeoffs involved to help support the decision-making process. MCDA has the advantage over less-structured decision-making methods due to its transparent methodology for combining heterogeneous data from disparate sources for and quantifying technical judgment and values and has been elevated as an important tool for nano-risk management (Linkow et al 2009; Fadel et al 2015). However, as noted by Hansen (2010) key issues in MCDA include who defines the decision criteria and how they are weighted and translated into numerical scores.

As we have showed in our analysis, several obstacles have to be overcome to facilitate decision-making about nano-enabled alternatives which are not present for chemicals. We therefore encourage the further development and incorporation of specialized tools into alternatives assessments, as well as case studies to explore their use when traditional methods are inadequate.

CONCLUSION

Alternatives assessment is a versatile and powerful tool for the comparative analysis of chemicals in order to identify safer options. The future design of products incorporating safer nanomaterials and the redesign of existing products with an emphasis on reducing the potential hazards for human health and the environment is key to the success of the innovations made possible through nanotechnology. In this paper, we have argued that the overall alternatives assessment approach, as evaluated based on the IC2 and NRC frameworks, is appropriate for nanomaterials. Yet some adaptations are needed as nanomaterials pose several methodological challenges.

First, alternatives assessment for nanomaterials is complicated by the sheer number of nanomaterials possible. This puts a demand on specific characterization of the materials in question and new, hitherto not included, characteristics are needed to strengthen the scientific foundations of specific alternatives assessment modules. While the links between physicochemical properties and hazards still remain to be explored for most nanomaterials, toxicity studies are presently available and can be used in alternatives assessment frameworks. For the time being alternatives assessments on nanomaterials should primarily be based on results of actual toxicity tests (including high throughput testing) rather than hazard extrapolations from inherent physico-chemical properties.

Second, nanomaterials clearly demonstrate the need for alternatives assessment methods to consider the intrinsic exposure potential as part of the comparative assessment process as there are distinct physicochemical properties as well as use characteristics that will distinguish which alternative (nano or bulk chemical) is fundamentally safer. The NRC and IC2 frameworks already include intrinsic exposure metrics that are sufficiently applicable for nanomaterials although new approaches from control banding tools developed for nanomaterials could be considered.

Third, the normal alternatives assessment hazard assessment module would likely fail to differentiate between different alternatives incorporating nanomaterials, since it may not adequately account for the differences in toxicity among similar materials with slightly different properties. However, in many cases it might be possible to make a generalized hazard assessment of the original nanomaterial of concern to identify endpoints of concern. The most effective path forward in the case of insufficient data might then be to compare the original nanomaterial with the identified alternatives with respect to the endpoint(s) of concern, with high throughput screening used to validate an alternative with reduced toxicity. If one alternative is not just a modified version of the original - a new generalized hazard assessment would have to be made to identify if that material is known to affect other endpoints. This does not, of course, ensure that no risk is present (not the objective of alternatives assessment) or that another, unknown, endpoint is not a concern. It only says that the alternative would be better for the investigated endpoint.

In nanotoxicology, how results of high throughput toxicity testing feed into risk assessment is still being debated – but perhaps high throughput data might feel much more at home for use in alternatives assessment as the decision-context is different. While traditional chemical risk assessment still is unfeasible for nanomaterials at large, alternatives assessment

could drive near-term decision-making about materials choices as well as incorporate mechanistic toxicity data to aid the selection of safer nanomaterials. However, any alternative assessment that considers nanomaterials should start like all others, first with considering the scope of the alternatives assessment and understanding the purpose of adding nanomaterials to serve the function at hand. Alternatives assessment aids in explicitly asking the question, "is this nanomaterial even needed". We encourage case studies of alternatives assessments that evaluate nanomaterials in order to further develop the necessary methods and to identify additional methodological needs going forward. We may still not in a position to fully predict or explain nanotoxicity, but perhaps the time is ready for making better and safer choices.

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DISCLAIMER

The authors declare that there are no conflicts of interest.

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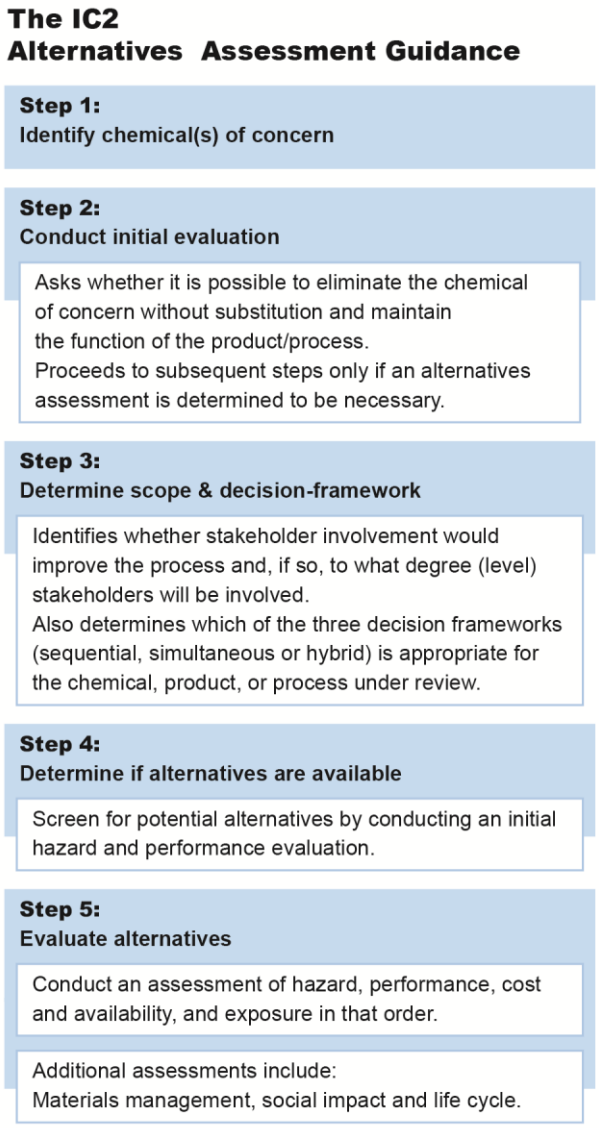

Figure 1: The IC2 Alternatives Assessment Guidance (IC2 2013)

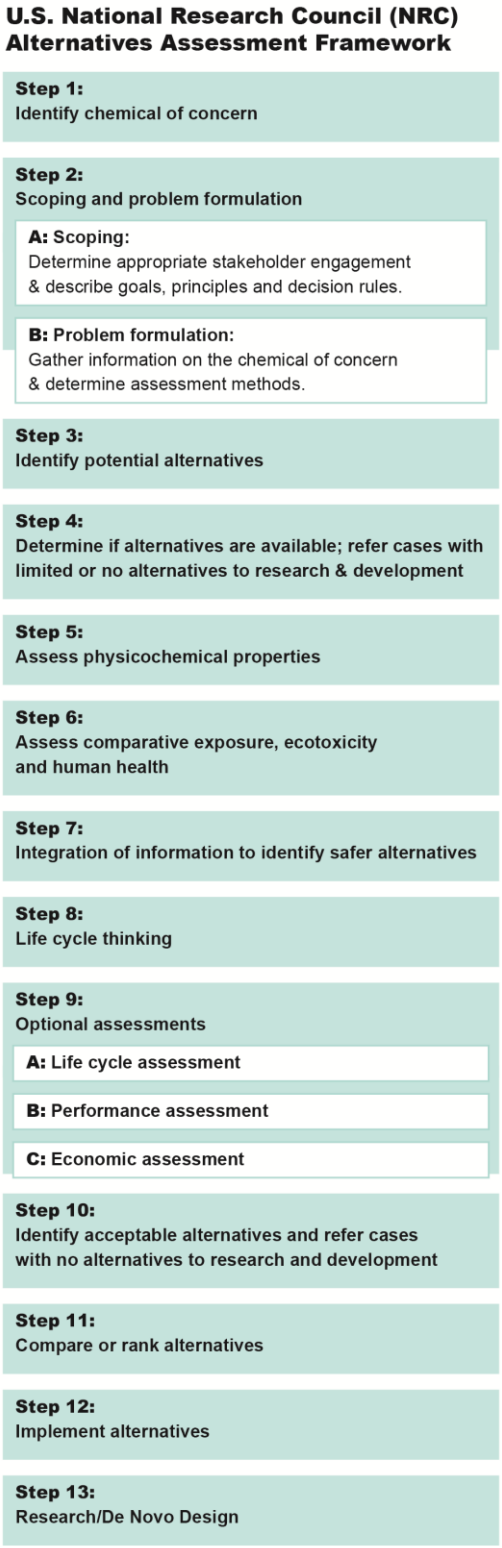

Figure 2: U.S. National Research Council (NRC) Alternatives Assessment Framework (NRC 2014)

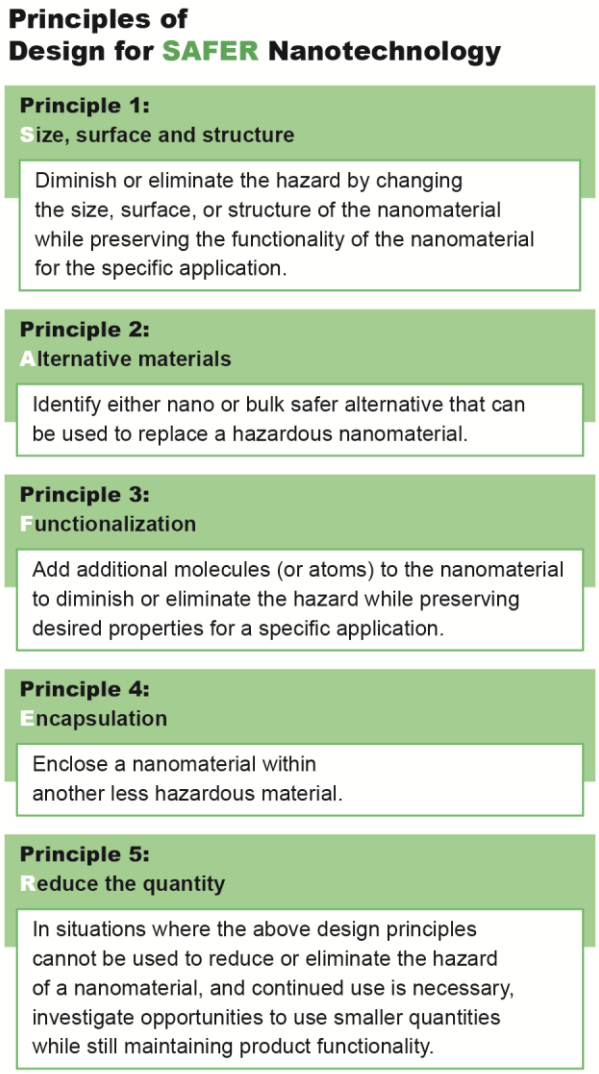

Figure 3: The 5 principles of design for safer nanotechnology (Morose 2010)

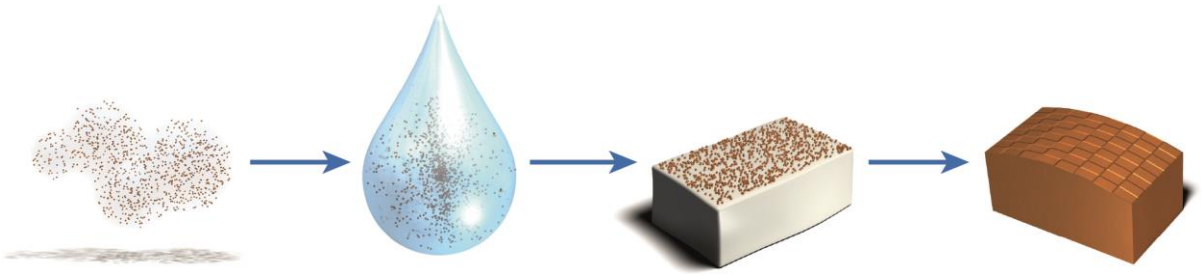

Figure 4: Changing the location of the nanomaterial in a given product or process will decrease the exposure potential. From left (high exposure) to right (low exposure): Airborne nanoparticles → nanoparticles suspended in liquids → surface bound nanoparticles → nanostructured surface.