Setting the stage for debating the roles of risk assessment and life cycle assessment of engineered nanomaterials

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While technological and environmental benefits are important stimuli for nanotechnology development, these technologies have been contested from an environmental point of view as well. The steady growth of applications of engineered nanomaterials has heated up the debate on quantifying the environmental repercussions. The two main scientific methods to address these environmental repercussions are risk assessment (RA) and life cycle assessment (LCA). The strengths and weaknesses of each of these methods, and the relation between them, have been a topic of debate in the world of traditional chemistry for over two decades. Here we review recent developments in this debate in general and for the emerging field of nanomaterials specifically. We discuss the pros and cons of four schools for combining and integrating RA and LCA and conclude with a plea for action.

Nanotechnology is rapidly evolving and is potentially capable of revolutionising many aspects of today's world. The world demand for nanomaterials is expected to reach $5.5 billion by 2016[1]. Manipulating matter at the nanoscale (1-100 nm) has provided a way forward in designing materials with unprecedented magnetic, electrical, optical, and thermal properties. In addition, engineered nanomaterials (ENMs) have been produced with the aim of enhancing people's lives, for instance by applying them in sunscreens, in self-cleaning facade coatings, and in clothing to reduce the numbers of microbes producing unwanted odors.

Although nanomaterials are perceived to improve environmental quality due to reduced material needs, human health and environmental safety concerns around nanomaterials have also been regularly voiced[2]. For example, silver nanoparticles used in socks to prevent the odors created by bacteria and fungi will sooner or later disappear into the drainage system through laundering[3], end up in municipal waste water treatment plants (WWTPs), and eventually emerge in streams, rivers, lakes, and oceans[4-6]. The resulting human health and environmental risks of nanosilver release in WWTPs and in the aquatic environment can be assessed by common risk assessment (RA) methods[7-9]. Another problem is that the production of silver nanoparticles for socks requires extra energy, e.g. for mining silver[5], compared to traditional socks without these particles. On the other hand, it has been argued that consumers may launder socks with silver nanoparticles less frequently than traditional socks[10], thus potentially saving energy and detergents. Such life cycle-related impacts and trade-offs can be assessed by life cycle assessment (LCA) methods. For all applications of

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nanomaterials, the environmental burden caused by nano-applications compared to similar traditional applications may increase in one part of the life cycle and decrease in another, and risks may increase or decrease at the same spots. Risks and life cycle-wide impacts also affect issues such as human health, ecosystem health and climate change, and trade-offs are commonly needed between these issues. Clearly, the environmental assessment of ENMs requires scientific, quantitative analyses, incorporating different perspectives, different environmental issues, and balancing costs and benefits. This gap can be filled by both RA and LCA, as they are both science-based quantitative analytical tools for policy support.

ENMs are regularly claimed to be more environmentally sustainable than traditional materials[11-13] without any supporting proof from proper research involving methods like RA and LCA. In addition, the environmental sustainability of ENMs should not just be assessed after they have entered the market, but rather in as early a stage of development as possible, to allow the assessment to still guide the technological development of these materials.

The relation between RA and LCA has been intensively discussed over the past two decades for traditional chemicals (e.g. pharmaceuticals, pesticides, metals)[14-16], as both RA and LCA can address the environmental consequences of technological solutions to societal issues. Relevant questions that have been raised many times include the following: should we do both an RA and an LCA, or is one of them sufficient? Can we integrate RA and LCA into a unified analysis? If we perform a separate RA and LCA, how should we deal with conflicting answers? This Perspective outlines the state of the debate on RA and LCA. We identify new elements of the debate for emerging technology systems, discuss possibilities and limitations of combining and/or integrating RA and LCA, and sketch the way forward. We use the application of silver nanoparticles in socks as an illustrating case study throughout the article.

Basics of risk assessment and life cycle assessment

RA has emerged as a scientific discipline and as a basis for regulatory decision-making[17-18]. RA refers to the quantitative and qualitative evaluation of the risk posed to human health and/or the environment by the presence of a particular contaminant or of mixtures of contaminants; see Figure 1[19]. A hazard refers to any potential to cause harm to humans or the environment[20]. Risk is defined as the probability that exposure to a hazard will lead to negative consequences for human health or the environment[21].

Exposure can be assessed by measuring environmental concentrations or by modeling the environmental fate of a contaminant, yielding a Predicted Environmental Concentration (PEC). Adverse effects are commonly expressed in terms of laboratory-derived dose-response relationships, which implies that effect assessment is the assessment of the causality between an organism’s exposure to a chemical and its response. Extrapolation of this causality to hitherto untested species allows a Predicted No Effect Concentration (PNEC) to be derived. Finally, RA involves assessing the PEC/PNEC ratio and quantifying its uncertainties. The RA paradigm of risk being proportional to the extent to which PEC/PNEC[22] values exceed 1 has been extensively validated for soluble chemicals[7,17].

There are no grounds to reject the paradigm for nanomaterials, albeit that it is essential to properly incorporate the characteristic features of nanomaterials in the RA. In this respect, the issue of dosimetry is key and a topical research area on how exposure levels should be expressed in terms of numbers of particles or the subsequent derived surface-volume area instead of on a mass hence concentration base[22-24]. Mode of actions of many nanoparticles are largely unknown and hence the shape of the dose-response relationships as well. We acknowledge that the type of a response of a chemical has huge impacts on the low effect levels (e.g. EC_1 to EC_{10}). In LCA often EC_{50} levels are used and these derived effect concentrations are less sensitive to the type of fit used, and are accurate irrespective of a non-carcinogenic or carcinogenic response. A similar line of reasoning is applicable for human RA of non-carcinogenic compounds, although with the key difference that PEC and PNEC are usually modeled in terms of daily intakes (PDI/ADI), with typical pathways of exposure through breathing, food consumption and drinking water contributing to intake.

Risk assessment has a key role to play as the scientific foundation for many national and international regulatory guidelines, as institutionalized by OECD, US-EPA and others. Concepts such as sustainability and the precautionary principle have gained increasing attention, aiming at prospective measures to decrease levels of risk. According to European regulators[25], nanomaterials in chemical substances must meet the requirements of the REACH regulation. To this end, modifications of some of the REACH annexes are envisaged[26], partly because the annexes fail to take into account the unique characteristics of ENMs and partly because of a lack of relevant data[22].

LCA in contrast offers a method for quantitatively compiling and evaluating the inputs, outputs, and potential environmental impacts of a product system throughout its life cycle[27]. LCA focuses on a product, technology, or function system, i.e. a system of economic or industrial processes needed for a product to function. System refers to the entire life cycle of a product. For example, for an ENM product system it includes the extraction and refining of all input materials, the production of the ENM itself, the application of the ENM in a specific product, the use and maintenance of that product, and so on, until the final disposal of the product at the end of its life, including options for recycling.

LCA also aims to include a broad range of impact categories, such as climate change, acidification, photochemical ozone formation, human toxicity, ecotoxicity, and resource depletion. There are different ways of defining and calculating these impact categories[28]. LCA can also map and balance environmental benefits, for instance more emissions or impact during production but less in the use phase, or more impact on climate change but less on resource depletion.

A broadly accepted set of principles for LCA is based on a series of standards issued by the International Organization for Standardization (ISO), the 14040 series[27,29]. This includes the LCA framework (Fig. 2). Examples of hypothetical LCA results are shown in Box 1.

LCA is widely applied today. It is used, for example, by companies[30-32], as well as to support eco-labeling schemes and environmental product declarations[33-34], and for public policy making[35]. It also constitutes the basis of the so-called “carbon footprint” to support performance-based regulations[36-37].

The fundamental constraint

The debate on the relationships between RA and LCA has been going on now for over two decades[38-42]. The main topics discussed include how RA expertise and models can be used within the framework of LCA[43-47], how to include metal-specific models[48], metabolites[49], spatial differentiation[50-54] and multi-substance impacts[55], and how to define and develop new approaches for pollutants is not yet covered[56-57]. As part of this discussion, the compatibility of RA and LCA has been intensively discussed[14-16,58-60]. It has been argued that it is fundamentally impossible to perform an RA within the framework of LCA.

We refer back to our case study on the application of silver nanoparticles in socks. Consider a world with a region of interest 'C' and a rest-of-world 'R'. There are two products in this world, socks and TVs. We concentrate on region C, and observe that the population wears socks and watches TV, both of which are imported from R. Both socks and TVs contain nanosilver. Some of the activities (industrial processes and consumer activities) emit CO_2 (blue arrows) while other activities emit nanosilver particles (orange arrows; Fig. 3, panel **a**). The main differences between RA and LCA are their starting point of analysis and time (see Box 2).

The present example is simplified, as the process of 'washing socks' belongs entirely to the life cycle of socks, whereas the process of 'using TVs' certainly does not. The process of 'generating electricity' works partly for the socks and partly for the TVs. If this process had emitted ENMs, we would have to allocate the emissions partly to the socks and partly to the TVs.

In conclusion, LCA cannot determine the PEC of nanosilver in region C, and as a result it cannot address risks. Instead, it gives an overall picture of the environmental burden from socks, due to nanosilver but also due to other pollutants (in this case CO_2), not only in the region where the socks are used, but also in the rest of the world. To emphasize the difference in meaning of "impact" between RA and LCA, impacts in RA have sometimes been labelled "actual", contrasting with those in LCA, which have been given the name "potential[43].

The example also shows that RA and LCA rely on the same sources of data, viz. processes (industrial and consumer activities) with emissions to the environment (Fig. 3, panel **b**).

Despite the fact that RA and LCA show fundamental differences (see above), RA expertise can still be usefully applied in LCA (see below).

Possibilities and limitations of combining and integrating

As discussed above, RA and LCA approach environmental issues from different perspectives, and they thus provide complementary information[61] and possibly lead to conflicting conclusions[42]. For instance, an RA with a focus on the laundry process and nanosilver might conclude that traditional socks are to be preferred over those containing nanosilver, whereas the LCA might end up with the opposite answer due to impacts related to the high energy use of the nanosilver production process and less laundry impacts due to the assumption that nanosilver socks are washed less.

Decision making always involves trade-offs, for instance between the economy and the environment. The use of complementary approaches implies that trade-offs are also possible *within* the environmental domain, namely between the risk perspective and the life cycle perspective. In addition, LCA itself already involves trade-offs, not between life cycle impacts and risks, but between different chemical emissions (more silver emissions, but less phosphate emissions due to less laundering), resource use (more silver ore for nanosilver socks but less phosphate rock), or impact categories (e.g., more global warming, less ecotoxicity). Since RA and LCA provide complementary information while representing two sides of the same coin, it is a relevant question how their results can best be combined, and how elements from one can be used in the other. Possibilities and limitations of combining and integrating RA and LCA have been explored by several authors over the past two decades. The debate on their results can be structured by distinguishing four 'schools of thought'. The four schools, modified on the basis of previous LCA-RA application reviews[16,42,60,62-64], serve to categorize most proposals in the literature; see Table 1.

Table 1. Summary of the four schools for combining and integrating LCA and RA.

Schools	Knowledge integration	Chain perspective	RA for LC hotspots	Combining results
RA performed	No	yes	yes	yes
LCA performed	yes	no	sometimes	yes

The Supplementary Information provides a more systematic overview of the literature on combining and integrating LCA and RA.

The first school is what we refer to here as 'knowledge integration'. Researchers within this school adopt specific elements of knowledge from RA into LCA's impact assessment phase. An early example is the approach of USES-LCA[46], where the USES model[65], which was developed for RA, was adapted to meet the requirements of LCA[43-44]. This idea has been further developed by many researchers in various ways (see section "The fundamental constraint of LCA compared to RA"). It must be stressed, however, that although using elements from an RA model in a different context may be useful in improving LCA, it lacks some of the strengths of RA. One example is the 'relative' nature of LCA, invalidating one of the purposes of RA, viz. that of being able to predict threshold exceedance[66]. Some authors[67-69] have tried to resolve this by using RA results (for instance, a PEC/PNEC-ratio as an indicator of threshold exceedance) to moderate LCA results. A second example concerns absolute versus relative risks. As an RA assesses absolute risks, it can work with safety factors to remain on the cautious side. Although this may lead to conservative results, it does not introduce bias. In LCA, the RA data are used to trade off risks. The absolute value is not important, but the relative value, in relation to other ENMs and to traditional chemicals, is[60,70].

The second school can be referred to as the 'chain perspective'. We adopt the term chain instead of life cycle to indicate that this school looks at a different 'life cycle' than the product life cycle that is central to LCA. Researchers in this school[65-74] include the life cycle of a chemical in an RA. However, the life cycle of a chemical is different from the life cycle of a product. The life cycle of a chemical includes all processes of all applications of the studied chemical, for example nanosilver, within a certain region; the life cycle of a product containing the studied chemical comprises of all processes (e.g. production, use and disposal of the nanosilver for socks) as allocated to that product (see Box 2), but also other processes needed for the functioning of the nanosilver socks, for instance the cultivation of cotton, production of fertilizers needed for that cultivation, transport of the cotton, etc. The EU REACH[7] regulation requires that RA is based on an assessment of the 'life cycle' of the chemical, which then includes its production, use and disposal. While this clearly makes sense when estimating the emission volume as a part of RA's exposure assessment[65], it overlooks parts of the life cycle where different chemicals are released (see Box 2). A clear example is the electricity production process, which is important in an LCA of nanosilver, but which is not part of the nanosilver's chain from an RA point of view.

The third school, referred to here as 'RA for LC-hotspots', starts from the opposite idea of including risks in a product life cycle. There are many proposals on this including life cycle risk assessment and life cycle based RA[68,75-83]. The basic idea is to first perform a full LCA and then do an RA for the dominant chemicals identified as part of the LCA (LC-hotspots). This then leads to more accurate impact assessments, as each process can be assessed on the basis of the local conditions (climate, population density, soil type, etc.)[42]. It could also yield an absolute assessment[84], in terms of 'actual impacts' rather than 'potential impacts[14]. However, there are still certain fundamental ('different perspectives' and 'real time versus virtual time') and practical limitations ('allocation') regarding the extent to which risks can be assessed in a life cycle context; see Box 2.

The fourth school, referred to here as 'combining results', aims to combine the results of RA and LCA, rather than combining or integrating parts of the analytical methods themselves. The results from LCA and RA can form the input for a procedure for multi-criteria decision-making (MCDM)[84-89].

Challenges for engineered nanomaterials

The four schools discussed above apply to traditional chemicals and products as well as ENMs and their product applications. ENMs are an example of an emerging technology[87], which means they are at an experimental stage with lab-scale experimental set-ups, or pilot-plant scales at best, and therefore create additional challenges to performing RA and LCA[54,88-89].

Firstly, as emerging technologies often only function at lab- or pilot-scale, data are also only available at these scales, and not at evidence-based full-market scales. Estimating the latter requires explorative scenarios of possible full-scale future applications of the technology studied[5,89-90]. Such scenarios then become the input for an RA and LCA. LCAs performed on emerging technology systems are often referred to as ex-ante or anticipatory LCAs[91-94].

Secondly, RA has to deal with the challenge of unknown environmental behavior of the product and unknown effects on humans and the environment of the ENMs themselves[95-96]. As the LCA impact modeling relies on RA expertise, nanoparticle impacts are often beyond the scope of present-day LCA studies[88,97].

Thirdly, complex technologies like nanotechnology require a larger supply chain and infrastructure than traditional technologies, while LCA databases are designed primarily for the latter ones. As an example, the widely-used ecoinvent LCA database[98] contains data about bulk materials and traditional equipment, such as steel, concrete, and rolling and crushing equipment, but not about nanomaterials, clean rooms and lithography machines. The result is that LCA studies on nanomaterials require explicit collection of data not only on the nanomaterials themselves, but also on the associated equipment. Another high priority is therefore the development of databases for the entire nanochain, from clean rooms to waste separation technologies[5,88-89].

Conclusions and outlook

We have shown that there is a fundamental constraint to combining and integrating RA and LCA, which hampers their full integration. Combining elements or results of RA and LCA is nevertheless useful and necessary. We have distinguished four different schools of thought for combining results of RA and LCA or integrating elements from RA into LCA and vice versa.

We conclude that all four schools represent valuable approaches to combining or integrating LCA and RA. We also conclude that it is not a matter of choosing between these schools but rather a matter of pursuing several of them. For example, both ‘knowledge integration’ and ‘combining results’ are required if we want to include system-wide trade-offs and risks in the environmental evaluation of ENMs. For the schools identified as ‘chain perspective’ and ‘RA for LC hotspots’, further clarification is needed as to how they can add to this evaluation, if they actually address other questions, or if they simply belong to one of the other two schools.

We have argued that the environmental evaluation of ENMs is not just a matter of RA or LCA, but that both methods are needed for a complete and comprehensive assessment of possible trade-offs and risks. As the specific use of both methods has been and is still being debated, clarity and a clear vocabulary are needed to structure the debate[60], achieve consensus, and effectively use the two tools while realizing their fundamental incompatibility. It is for this purpose that we have postulated the above classification into four schools, and described a number of incompatibilities between RA and LCA in detail. We welcome further inputs to this debate, and realize that this will definitely not be the final word on this matter.

Finally, realizing that all human activities lead to some level of environmental impact and that the level and seriousness of these impacts should rather be assessed ex-ante than ex-post[99-100], a specific challenge for ENMs is in combining and/or integrating RA and LCA even when the ENM systems and their properties are not yet well known. Collaboration between the fields of RA and LCA is of the utmost importance to effectively address this challenge, and to use RA and LCA for ex-ante technology assessments and the timely identification or resolution of environmental issues. The RA and LCA communities should collaborate intensively on procedures to estimate the unknown data, including proper uncertainty assessments, defining and developing approaches for modeling of as yet unclear impacts, co-developing better methods for impacts already covered, and estimating LCA data for the most crucial processes in the environmental evaluation of ENMs. Alternatively, we could just wait until all data and models are available. By then, however, most nanomaterials will already have been fully marketed, implying that all systems have already been designed, with no way back[101]. The choice is ours.

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Competing financial interests

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Figure 1 | The general methodological framework for RA distinguishing the four main phases of environmental RA: hazard identification (establishing if there is a risk present), exposure assessment (predicted environmental concentration (PEC) or daily intake (PDI)), effect assessment (establishing critical levels of exposure: predicted no effect concentration (PNEC) or acceptable daily intake (ADI)), and risk characterization (calculating the PEC/PNEC or PDI/ADI quotient). Figure adapted from ref. 19.

Figure 2 | The general methodological framework for LCA distinguishing four main phases: goal and scope definition (establishing the aim, the functional unit as a basis for the comparison, and the scope of the intended study), inventory analysis (compiling and quantifying inputs and outputs for a product), life cycle impact assessment (understanding and evaluating the magnitude and significance of the potential environmental impacts), and life cycle interpretation (evaluating the findings in order to reach conclusions and recommendations). The red arrows indicate the result of the inventory analysis as input for impact assessment or interpretation, the blue arrows the result of the impact assessment. Figure adapted from ref. 27.

Figure 3 | Example illustrating the fundamental differences between RA and LCA using the application of silver nanoparticles in socks as a hypothetical case study.

Box 1 | LCA results comparing nanosilver containing socks with traditional socks

Suppose two pairs of socks are compared using LCA, and adopting as the functional unit '1 year of wearing clean socks'. The technical assumptions made for this comparison might include the following:

	traditional socks	nanosilver socks
lifetime of socks (yrs)	1	3
washings per week	3	1
temperature of washing (˚C)	40	30
Etc.	…	…

The inventory table, which is the result of the inventory analysis (see red arrow in Fig. 2), might look as follows:

emissions / resource uses	traditional socks	nanosilver socks
CO_2 to air (kg)	25	20
SO_2 to air (kg)	0.4	0.2
Phosphate to water (g)	60	20
Nanosilver particles to water (µg)	0	0.01
Crude oil from earth (kg)	3	4
Silver ore from earth (mg)	0	1
Etc.	…	…

The characterization results, which are the most important results of the impact assessment phase (see blue arrow in Fig. 2), might look as follows (using dichlorobenzene (DCB) as a reference compound for toxicity assessment):

impact categories	traditional socks	nanosilver socks
Climate change (kg CO_2-eq.)	25	20
Aquatic ecotoxicity (kg DCB-eq.)	10	35
Human toxicity (kg DCB-eq.)	45	43
Aquatic eutrophication (kg PO_4^{3-}-eq.)	5	1
Depletion of fossil fuels (MJ)	3	6
Etc.	…	…

Box 2 | The fundamental differences between RA and LCA

Different perspectives: RA typically focuses on the risk (interpreted as the extent to which the PEC/PNEC ratio exceeds 1; see above) of a specific chemical in a specific region, resulting from its measured or predicted use and release. For instance, it addresses the risks of nanosilver in region C (Fig. 3). Assuming that there is no transboundary pollution of nanosilver, the RA addresses only the emissions from washing socks and using TVs. Supposing that the region's emission of nanosilver from washing 130,000,000 kg of socks/yr is 25 kg/yr, and the region's emission of nanosilver from using 1,450,000 TVs/yr is 15 kg/yr, so a total of 40 kg/yr. This is the result of the emission assessment, and will form the basis of the PEC. It may be used to decide if a critical concentration (PNEC) will be exceeded or not.

The LCA perspective typically starts with a functional unit, say 1 pair of socks, regardless of the number of socks in use. The socks will have a life cycle emission of nanosilver during manufacturing (say 1 mg), during washing (5 mg), and during disposal (2 mg), so a total of 8 mg per pair of socks. This 8 mg cannot be compared with a critical threshold, for several reasons:

- Only real-time (see below) emission flows (in kg/yr), not emission quantities (in kg), will lead to a steady-state concentration (PEC).
- The functional unit of 1 pair of socks is completely arbitrary, and we might just as well have taken 1,000 pairs of socks, or 1 billion pairs of socks.
- The calculated emission of 8 mg is scattered across the region of study and the rest of the world.
- The calculated emission of 8 mg is also distributed over a long period of time (there may be several years between manufacture and disposal of the socks).
- By studying the life cycle of socks, we are overlooking the other source of nanosilver in region C, namely TVs.

Real time and virtual time: With respect to the first bullet, note that LCAs are typically performed in terms of 'per unit of product'. If an industrial process emits x kg/yr and produces y product units/yr, LCA eliminates the time unit:

$$\frac{\text{emission}}{\text{unit of product}}(\text{kg/unit}) = \frac{\text{emission rate (kg/yr)}}{\text{production rate (unit/yr)}} = \frac{x}{y}$$

RAs, on the other hand, are based on real-time steady-state emission rates (y), yielding steady-state concentrations (PEC).

Some of these problems might be overcome by adopting a new LCA paradigm, for instance by taking a functional unit with a flow character (pairs of socks per year; bullet 1), and using the real number (130,000 tons of socks; bullet 2). Indeed, with a functional unit of 130,000,000 kg of socks/yr, some of the limitations will be removed. Starting from the total use of socks in region C per year, the resulting nanosilver emissions may reflect the real-time yearly emission for the washing process. However, this is not the case for the nanosilver emissions due to any upstream or downstream processes, such as the production process, as we are not considering their total process flows but only the quantity needed for producing the nanosilver socks. The total number of socks introduces a time dimension to these upstream processes but this reflects a virtual time rather than real-time. Moreover, by concentrating on a product (socks), all activities that do not relate to socks (such as those relating to TVs) are ignored and we will still do not obtain a proper estimation of the concentration of nanosilver in the region (bullet 5).